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(54) **CRYSTAL FORMS OF TETRAHYDRO-N, N-DIMETHYL-2, 2-DIPHENYL-3-FURANMETHANAMINE, PROCESSES OF MAKING SUCH FORMS, AND THEIR PHARMACEUTICAL COMPOSITIONS**

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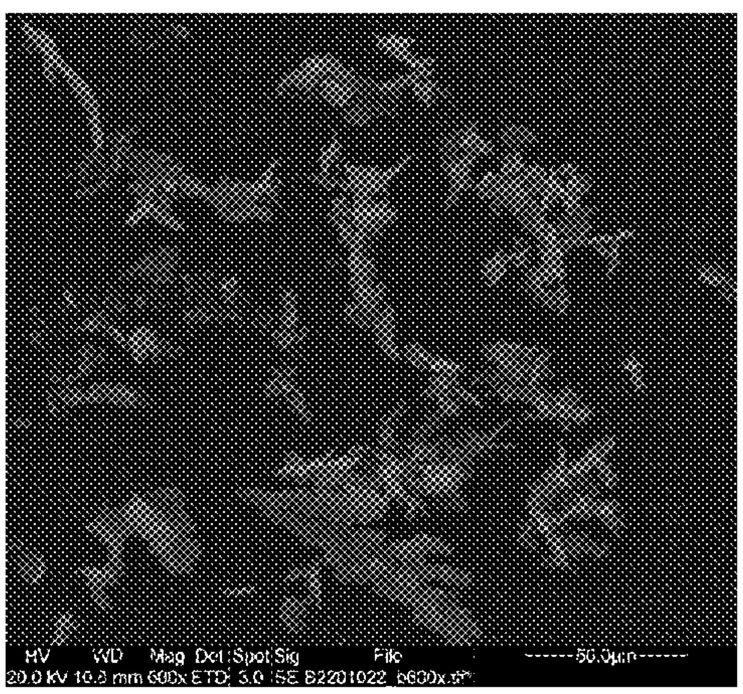
B01D 9/00	(2006.01)

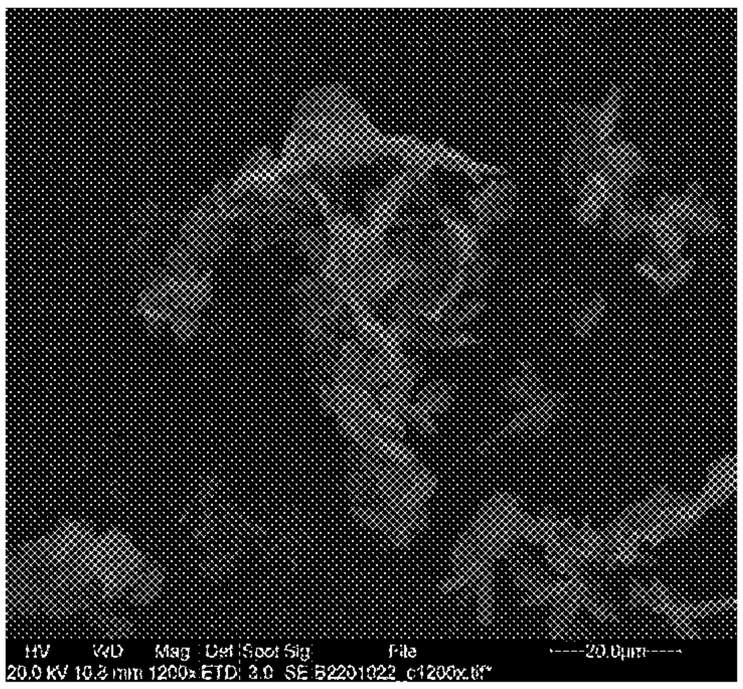
(52) **U.S. Cl.**

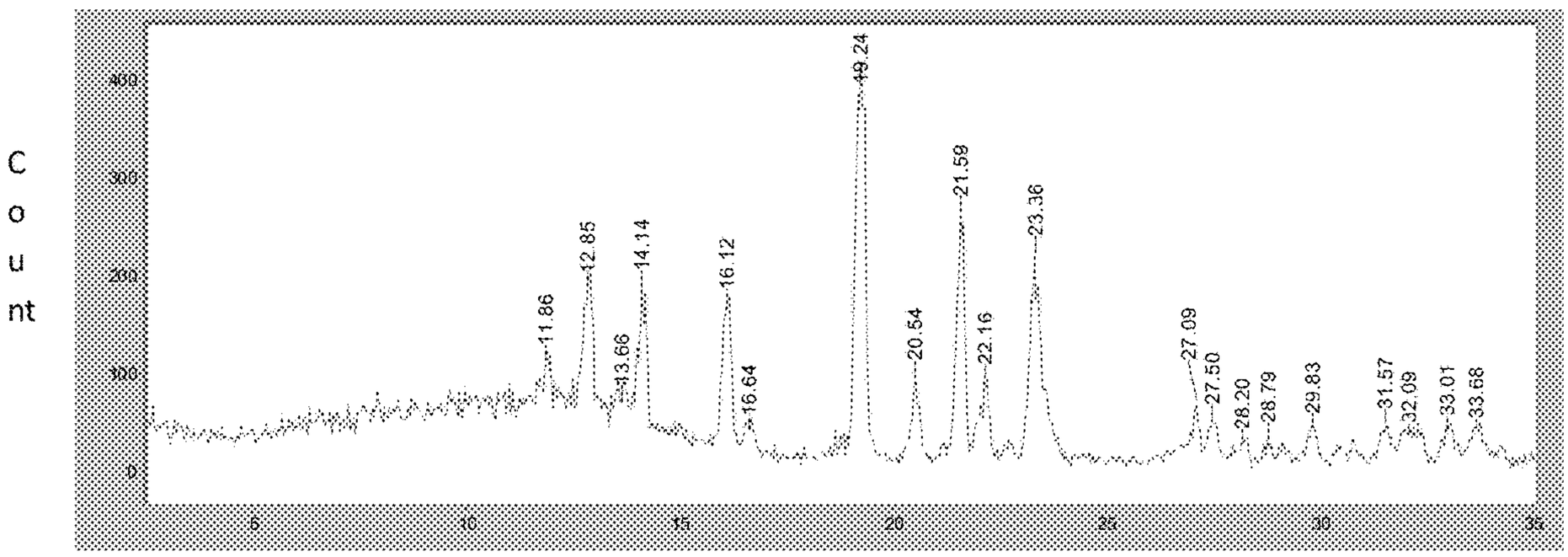
CPC ***C07D 307/14*** (2013.01); ***B01D 11/0411*** (2013.01); ***B01D 9/005*** (2013.01); ***B01D 11/0403*** (2013.01); *A61K 31/341* (2013.01)

(57) **ABSTRACT**

Polymorphic forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) and a metabolite of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX19-144) are disclosed and characterized. Compositions and method for treatment of Alzheimer's disease that includes the polymorphic forms and metabolite of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73).



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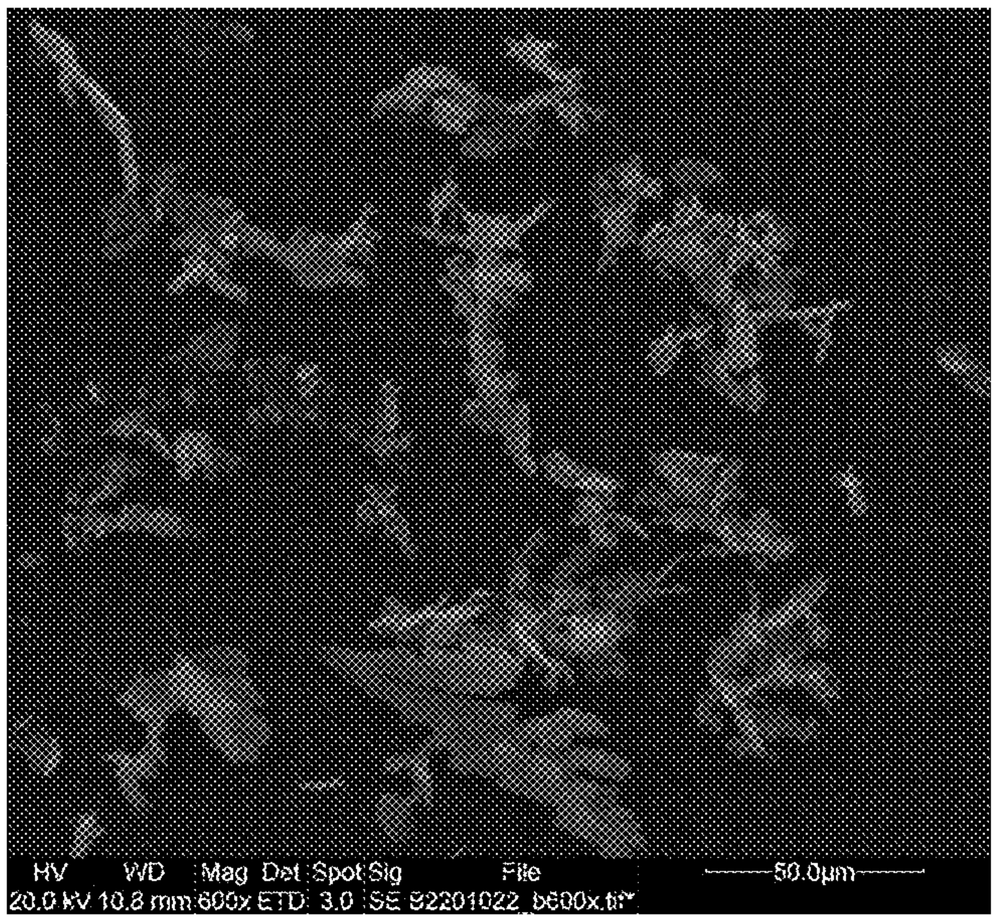
23.36
27.09
27.50
28.20
28.79
29.83
31.57
32.09
33.01
33.68
5
10
15
20
25
30
35
2-theta value

FIG. 1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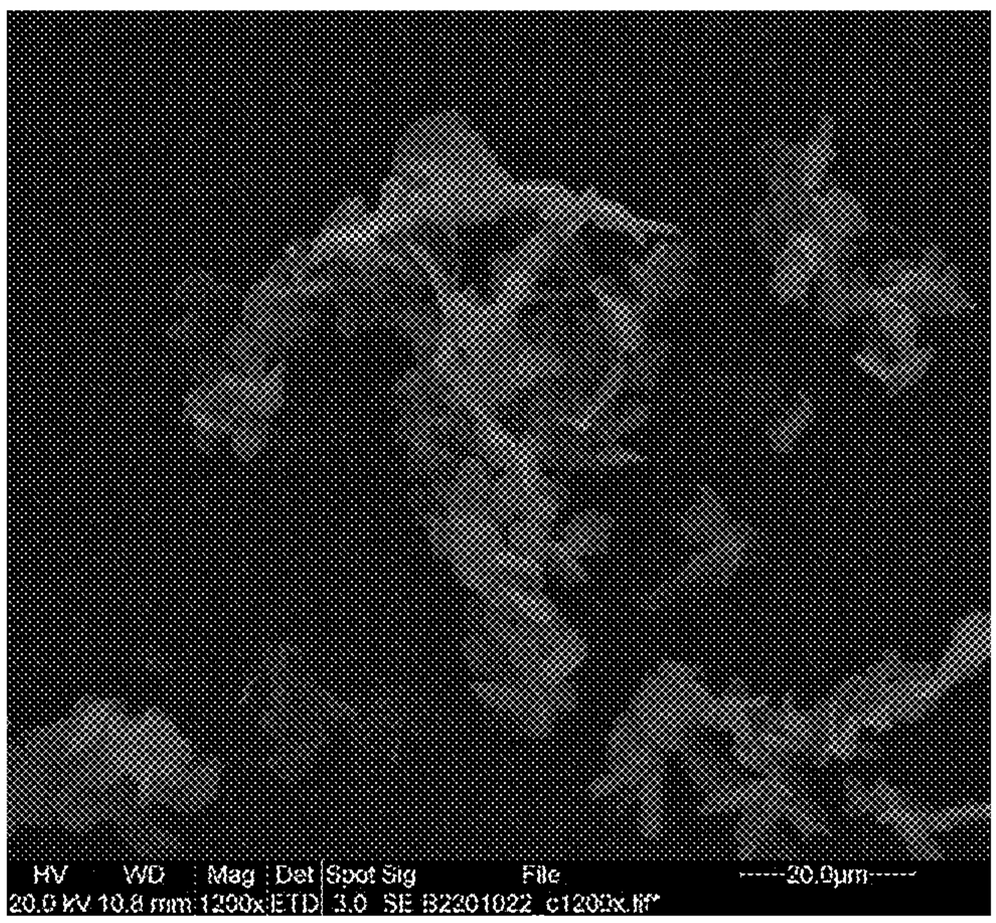
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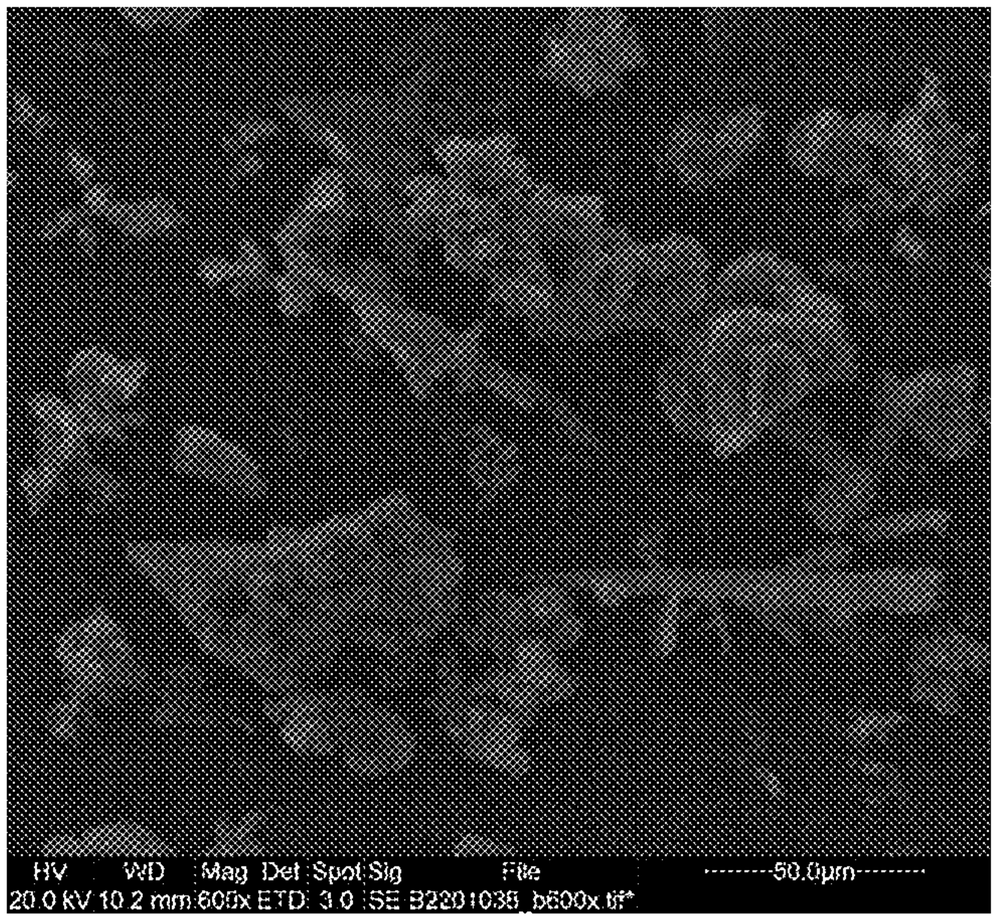
20.0µm

FIG. 2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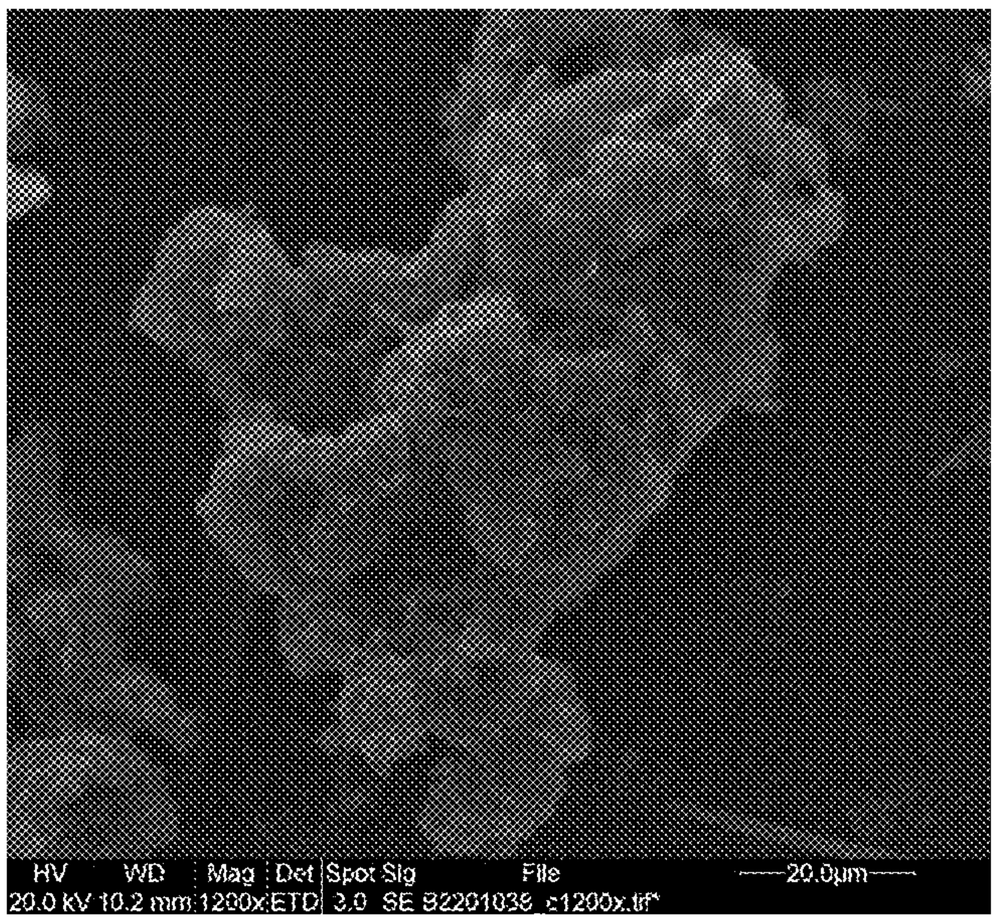
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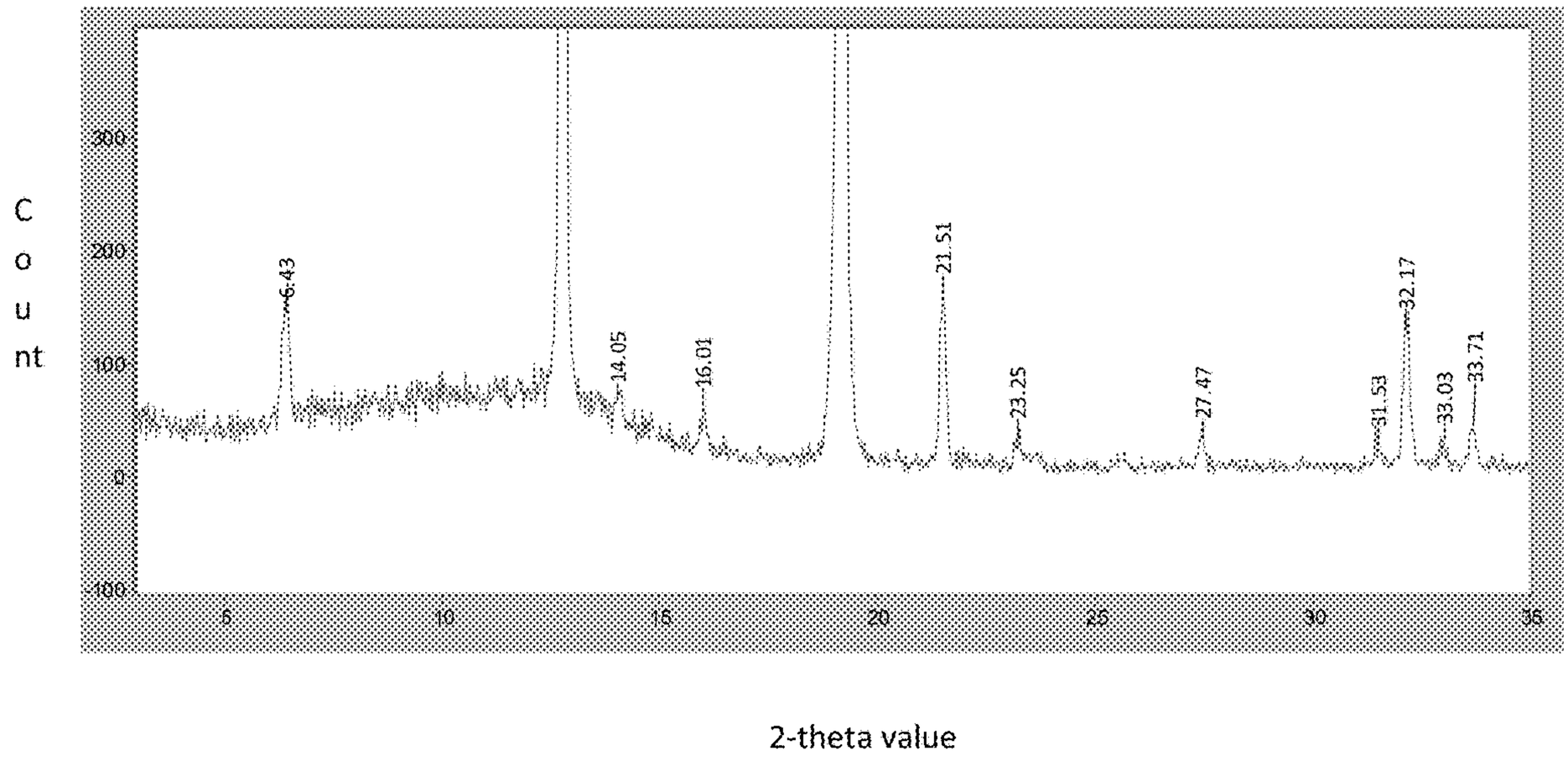
FIG. 3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21.51
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27.47
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33.03
33.71
5
10
15
20
25
30
35
2-theta value

FIG. 4

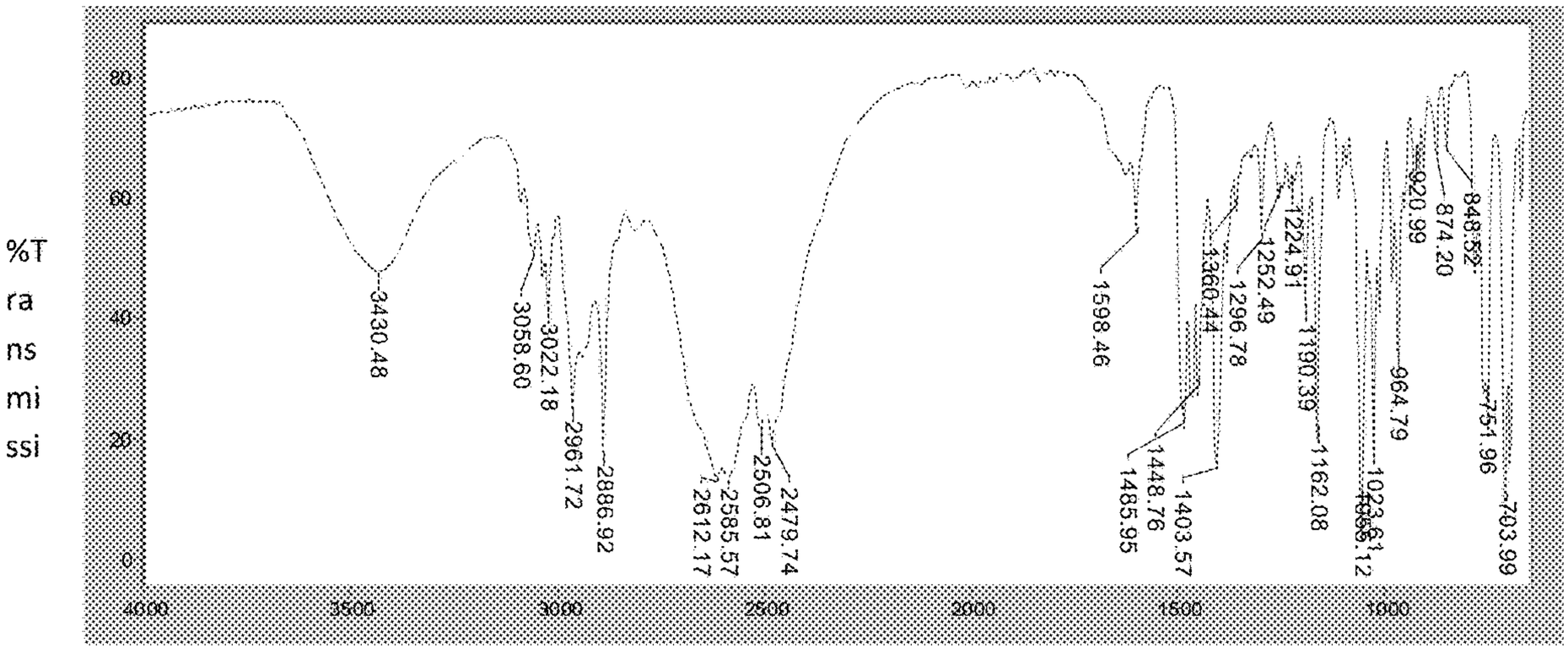
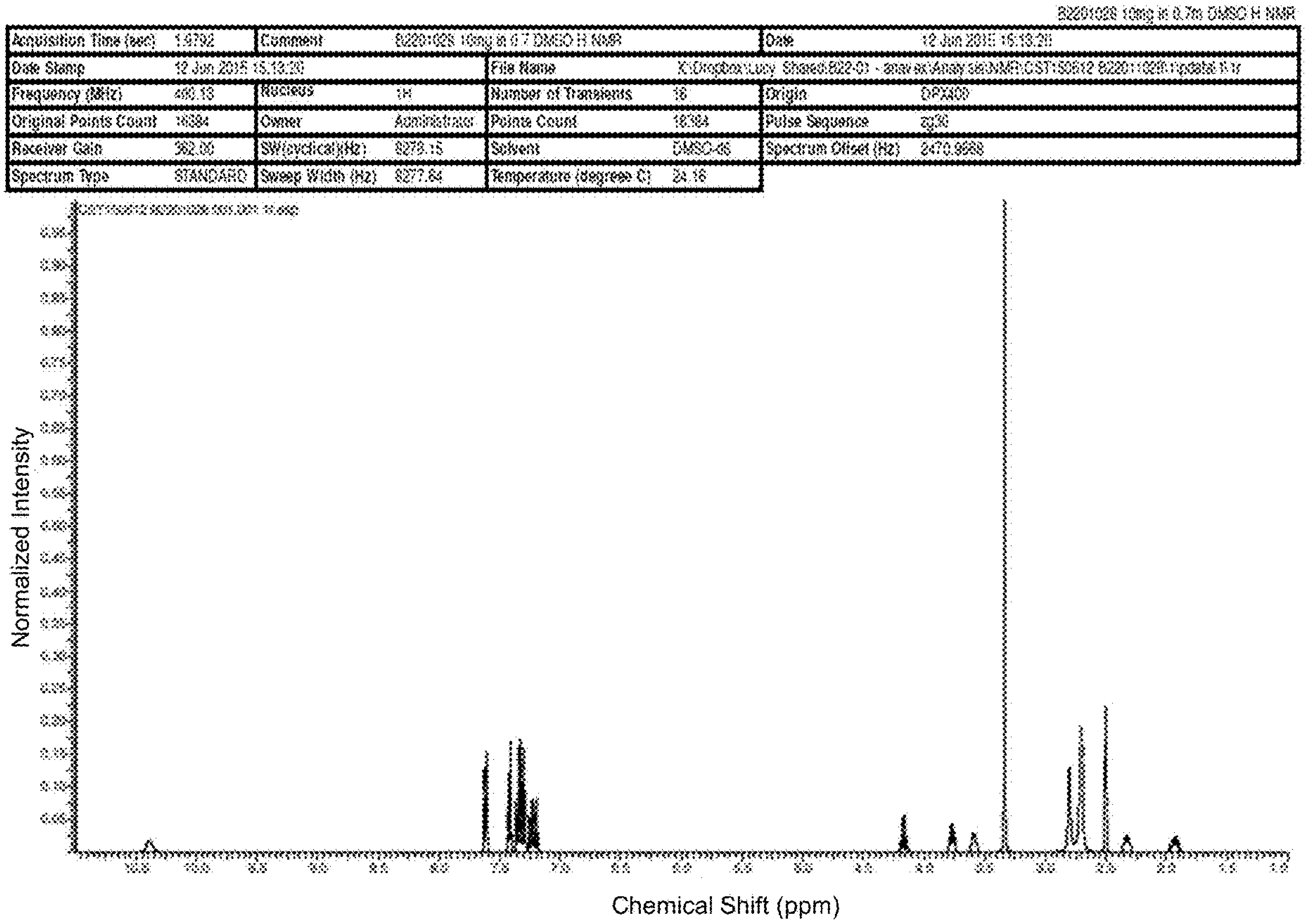

%Transmissi
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
3430.48
3058.60
3022.18
2961.72
2886.92
2612.17
2585.57
2506.81
2479.74
1598.46
1485.95
1448.76
1403.57
1360.44
1296.78
1252.49
1224.91
1190.39
1162.08
1088.12
1023.61
964.79
920.99
874.20
848.52
751.96
703.99
Wave number cm-1

FIG. 5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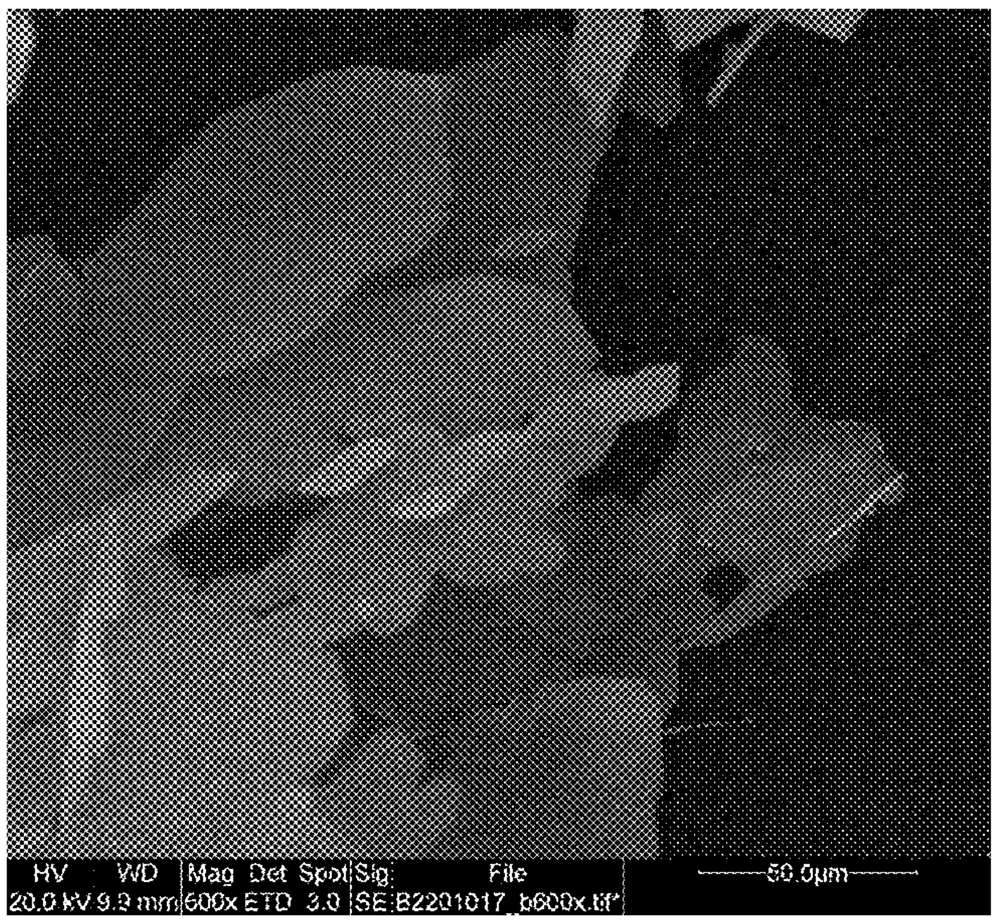
Acquisition Time (sec) 1.9792
Comment B220102B 10mg in 0.7 DMSO H NMR
Date 12 Jun 2015 15:13:20
Date Stamp 12 Jun 2015 15:13:20
File Name
Frequency (MHz) 400.13
Nucleus 1H
Number of Transients 16
Origin DPX400
Original Points Count 16384
Owner Administrator
Points Count 16384
Pulse Sequence zg30
Receiver Gain 362.00
SW(cyclical)(Hz) 8278.15
Solvent DMSO-d6
Spectrum Offset (Hz) 2470.9688
Spectrum Type STANDARD
Sweep Width (Hz) 8277.64
Temperature (degree C) 24.16
Normalized Intensity
Chemical Shift (ppm)

FIG. 6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Mag Det Spot Sig File
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50.0µm

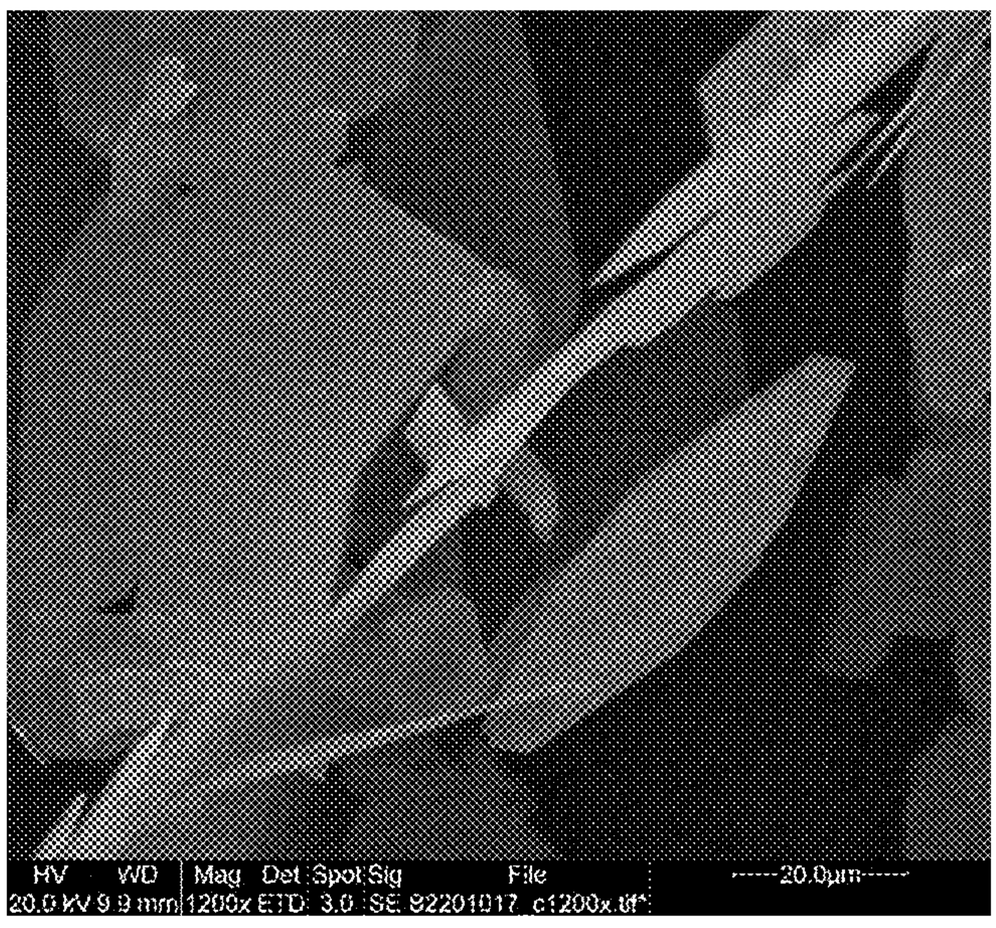
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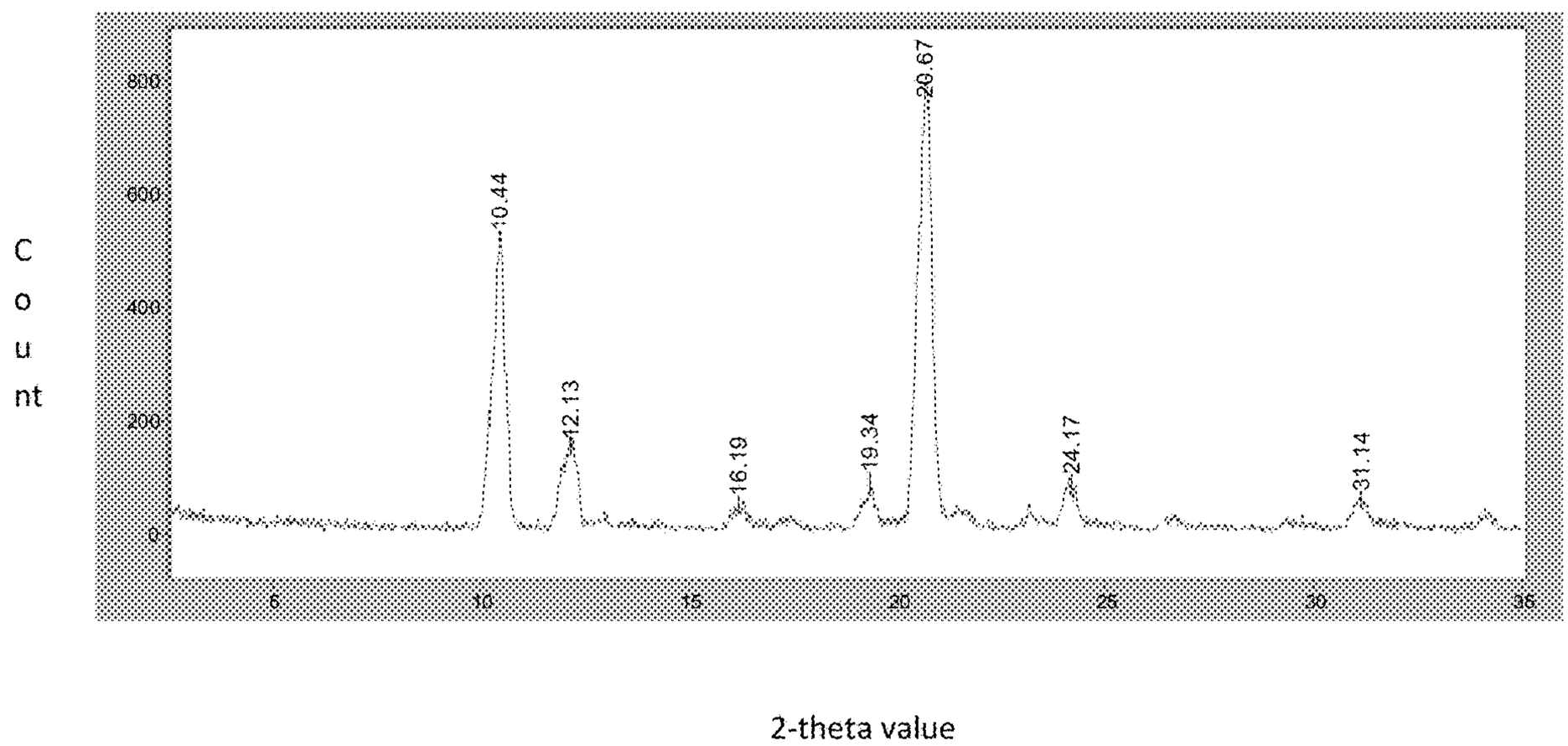
FIG. 7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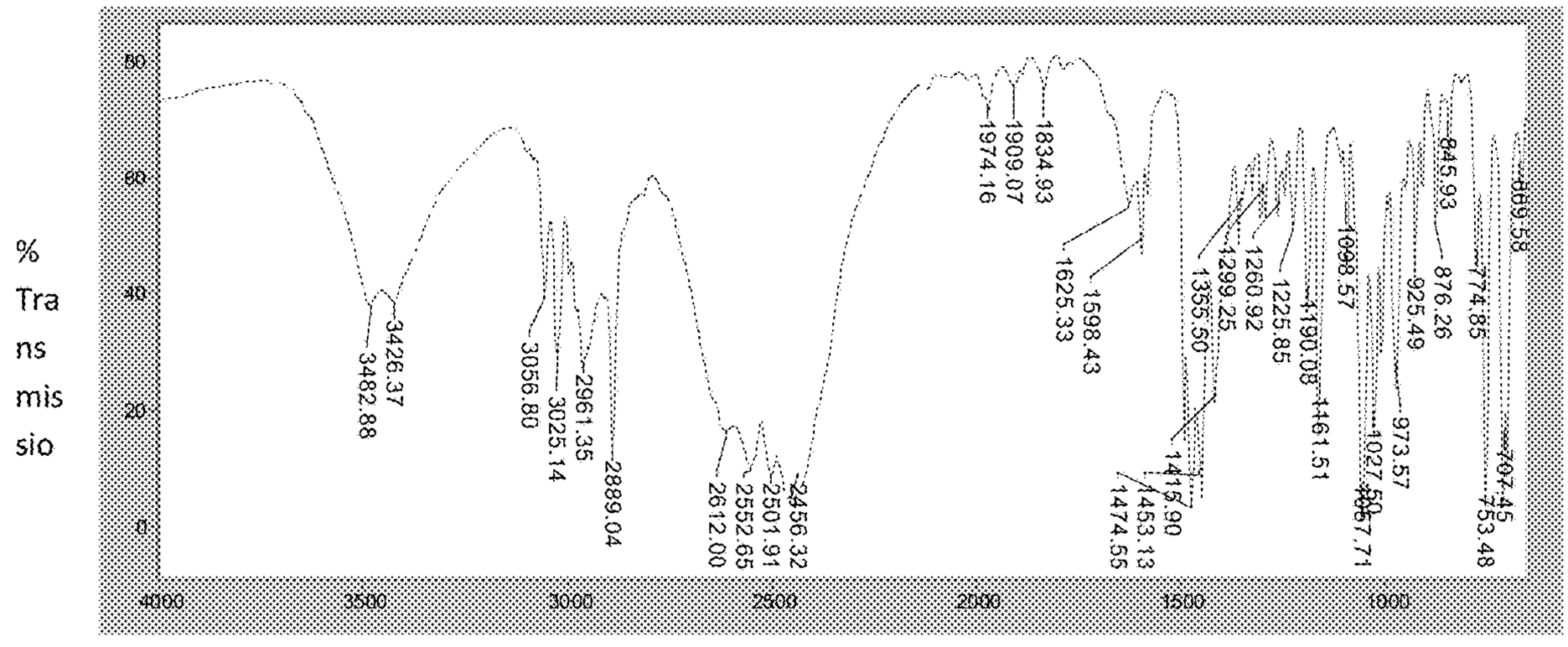
31.14
5
10
15
20
25
30
35
2-theta value

FIG. 8


%
Tra
ns
mis
sio
80
60
40
20
0
4000
3500
3000
2500
2000
1500
1000
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3426.37
3056.80
3025.14
2961.35
2889.04
2612.00
2552.65
2501.91
2456.32
1974.16
1909.07
1834.93
1625.33
1598.43
1474.55
1453.13
1415.90
1355.50
1299.25
1260.92
1225.85
1190.08
1098.57
1027.50
973.57
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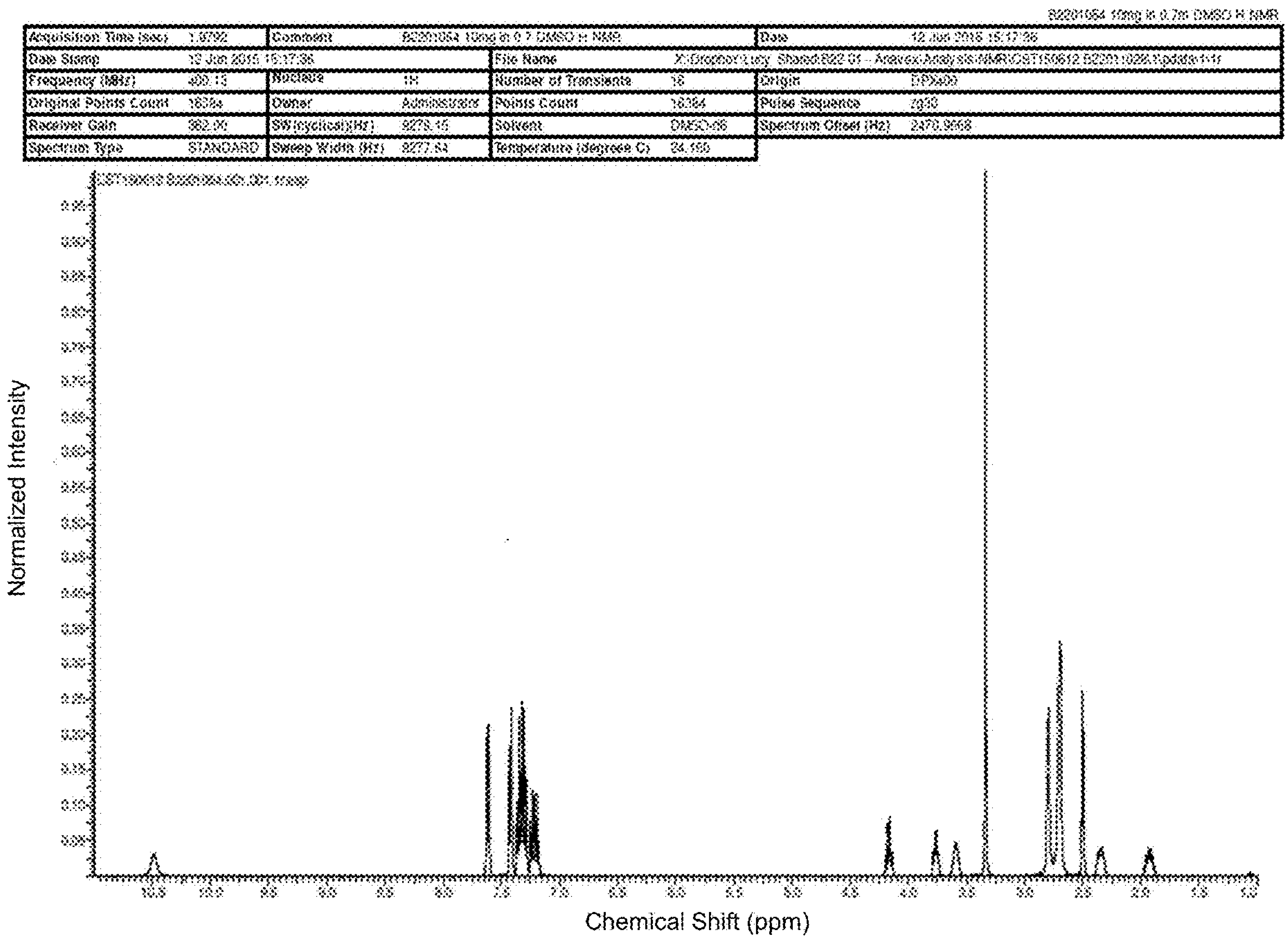
461.51
457.71
Wave number cm-1

FIG. 9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Date Stamp
File Name
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Number of Transients
16
Origin
Original Points Count
Owner
Administrator
Points Count
16384
Pulse Sequence
zg30
Receiver Gain
SW(cyclical)(Hz)
Solvent
DMSO-d6
Spectrum Offset (Hz)
2470.9668
Spectrum Type
STANDARD
Sweep Width (Hz)
Temperature (degree C)
Normalized Intensity
Chemical Shift (ppm)

FIG. 10


HV WD Mag Det Spot Sig File 50.0µm
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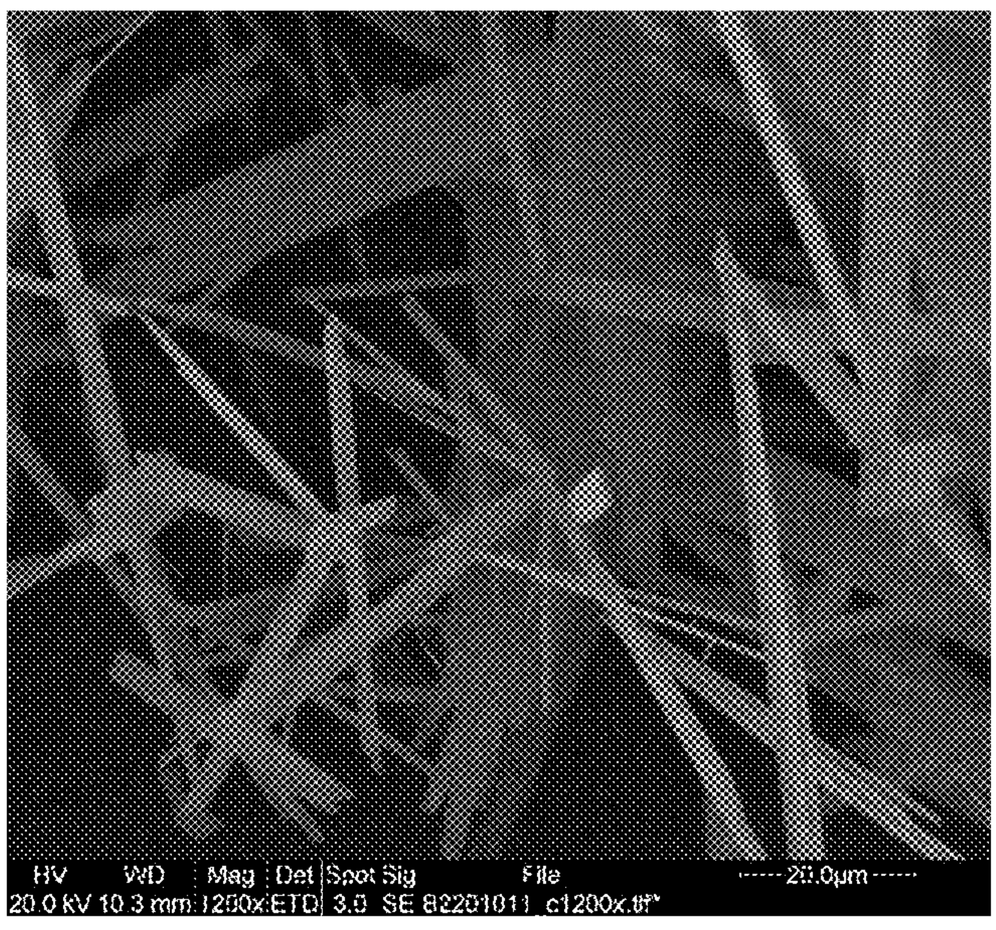
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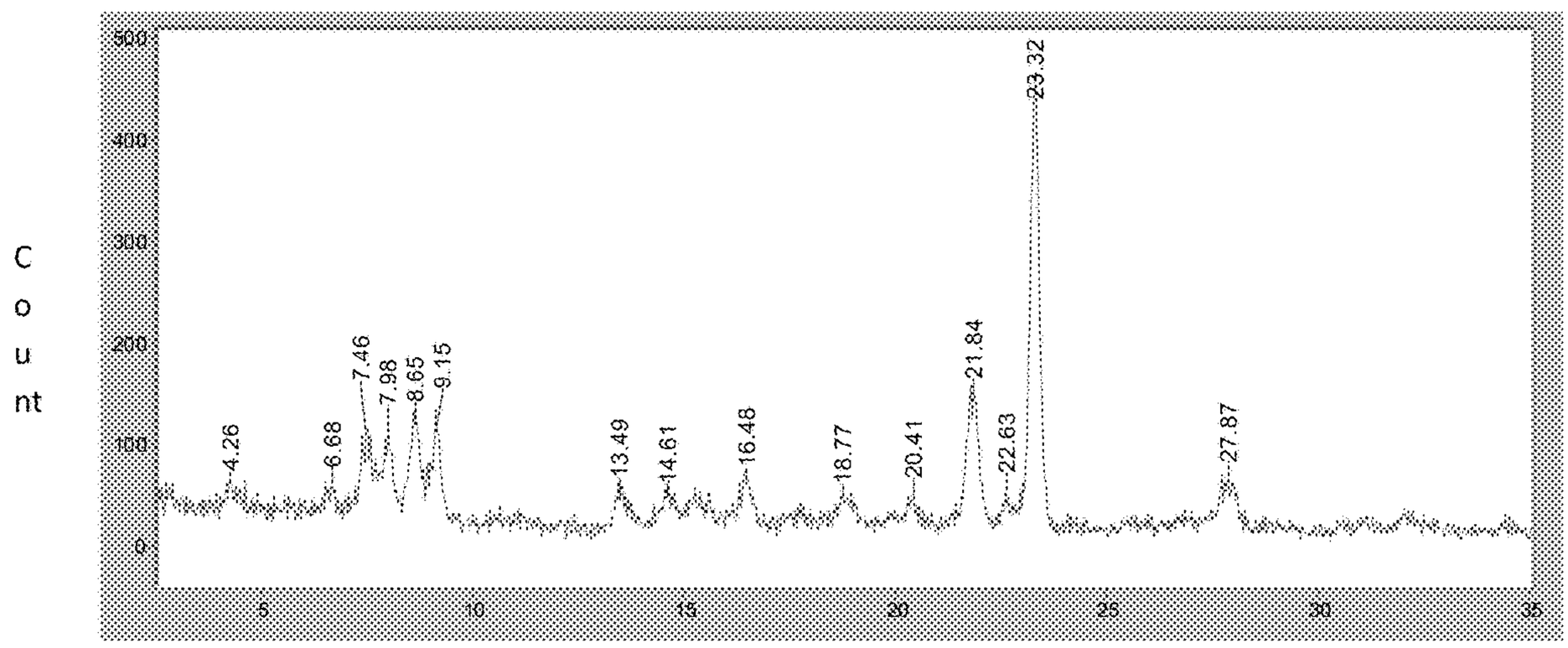
FIG. 11


Count
2-theta value
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400
300
200
100
0
5
10
15
20
25
30
35
4.26
6.68
7.46
7.98
8.65
9.15
13.49
14.61
16.48
18.77
20.41
21.84
22.63
23.32
27.87

FIG. 12

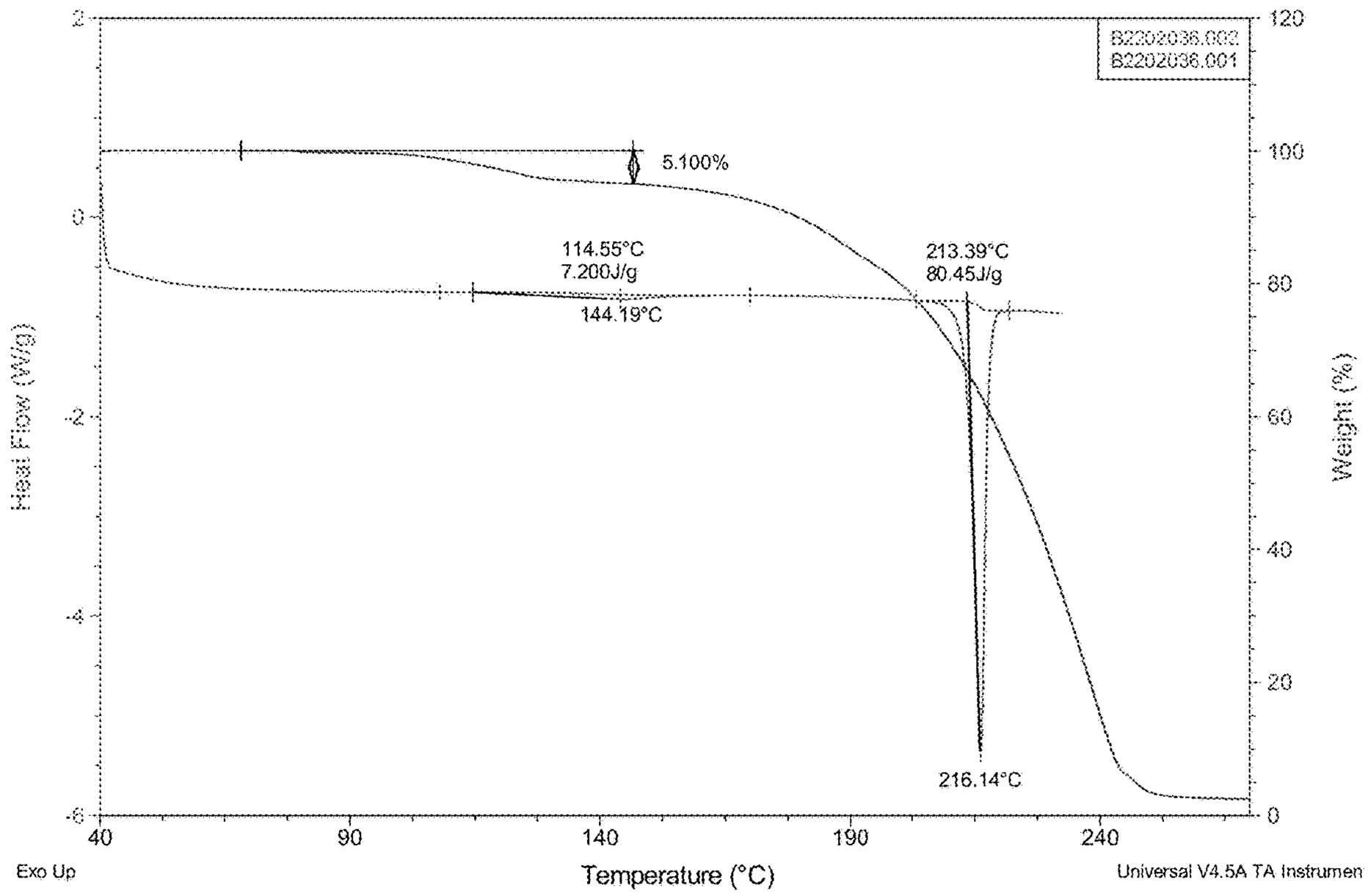
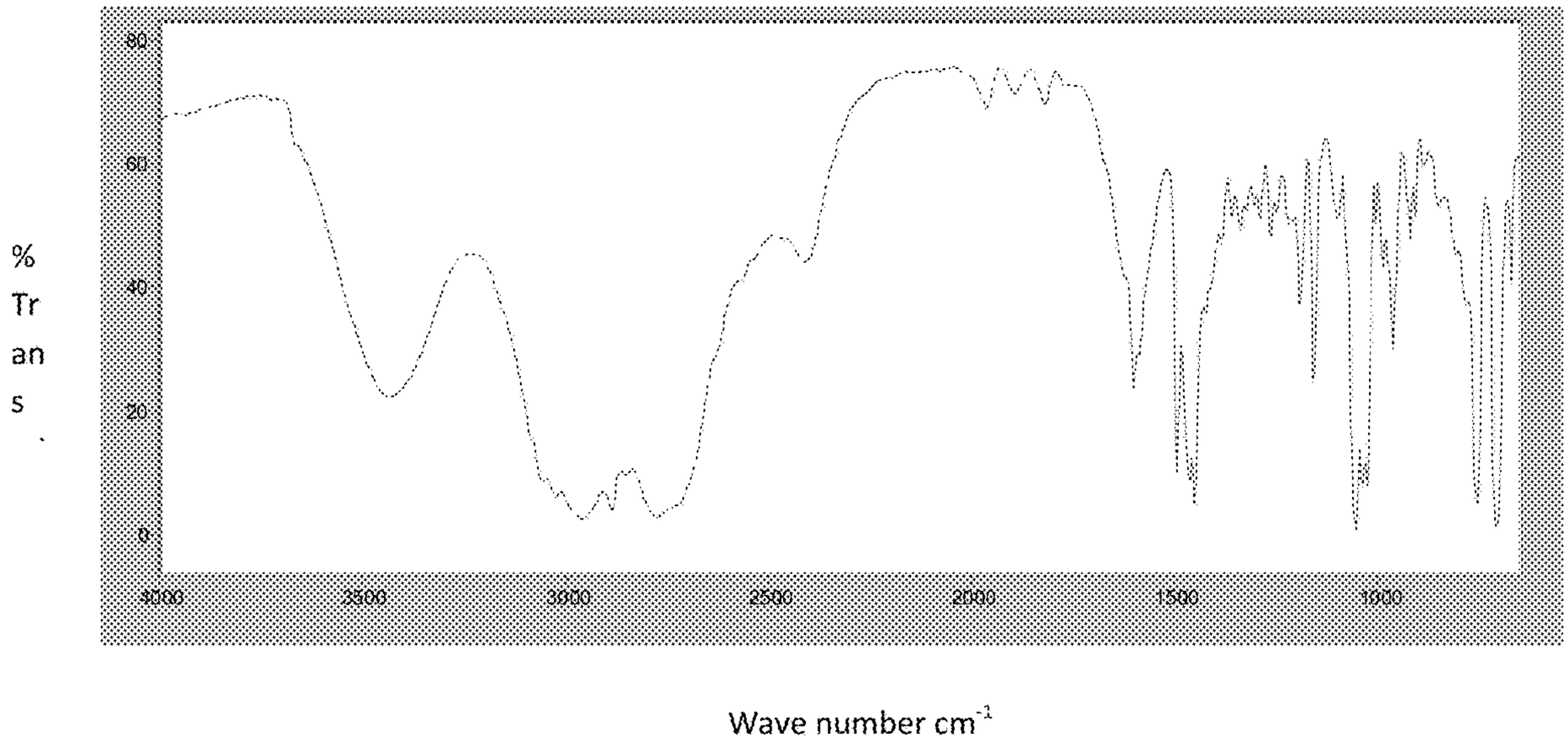

B2202036.002
B2202036.001
5.100%
114.55°C
7.200J/g
144.19°C
213.39°C
80.45J/g
216.14°C
Heat Flow (W/g)
Weight (%)
Temperature (°C)
Exo Up
Universal V4.5A TA Instrumen
2
0
-2
-4
-6
120
100
80
60
40
20
0
40
90
140
190
240

FIG. 13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% Trans
4000
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3000
2500
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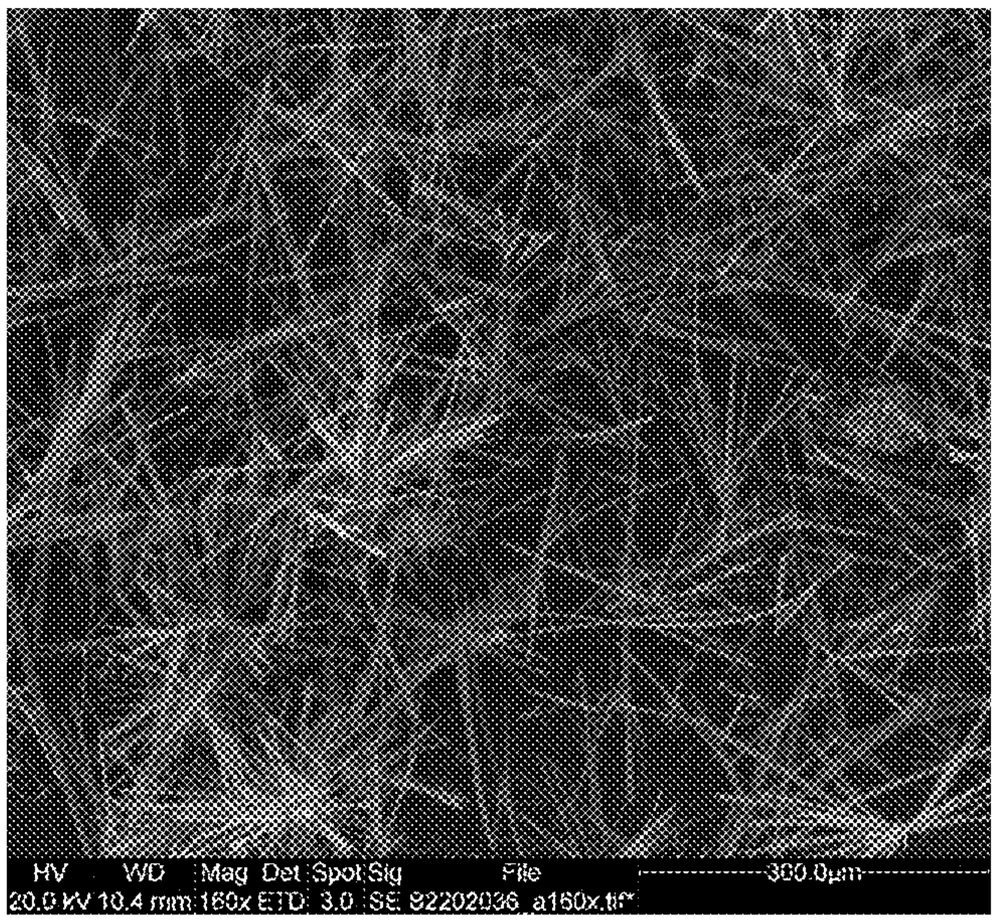
1500
1000
Wave number cm-1

FIG. 14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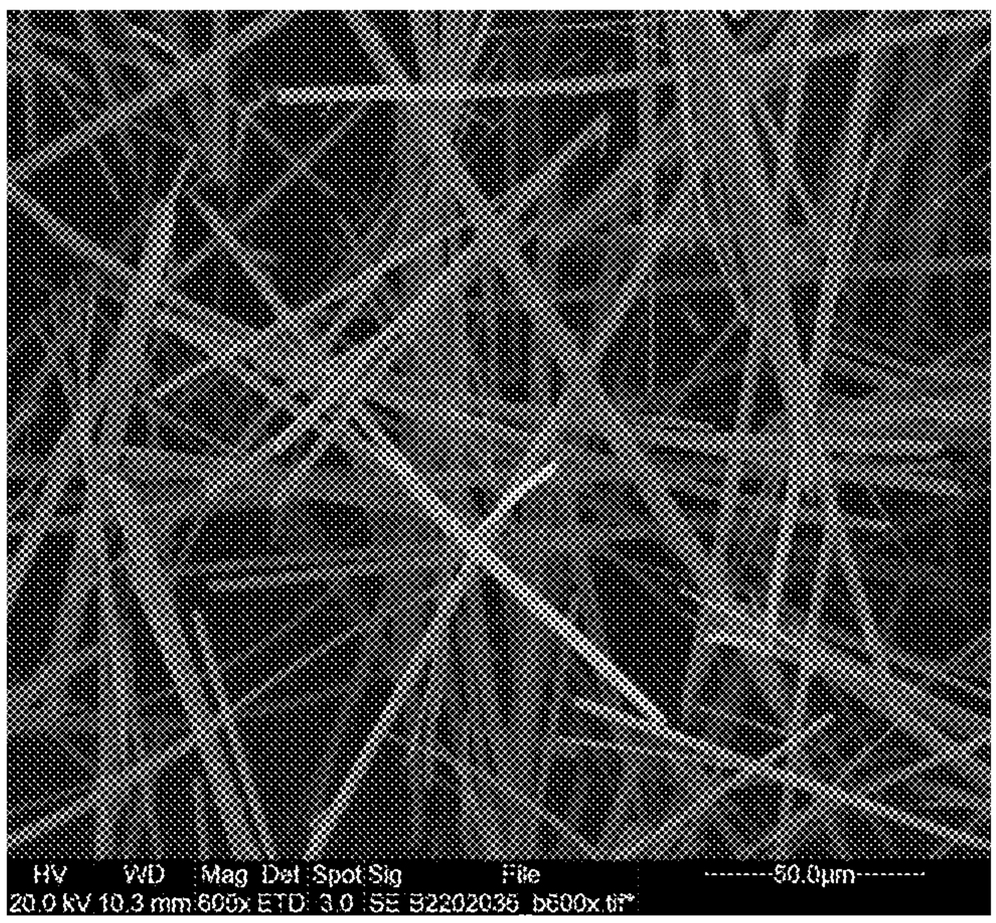
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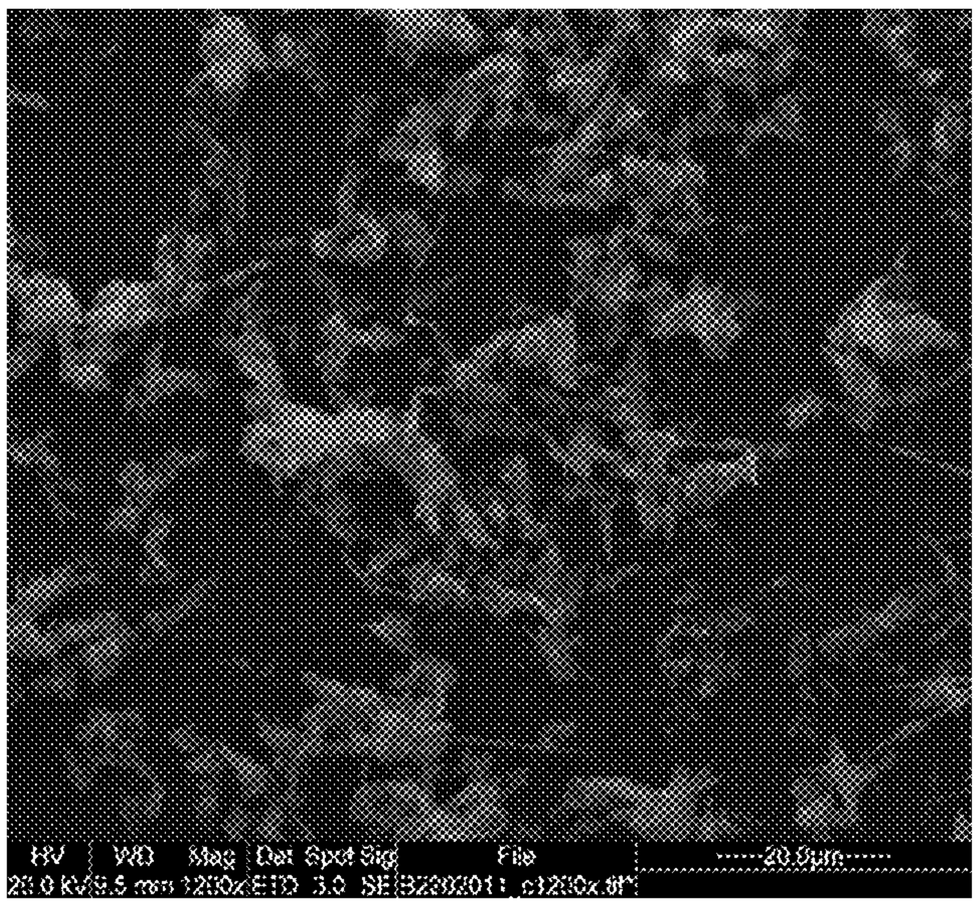
FIG. 15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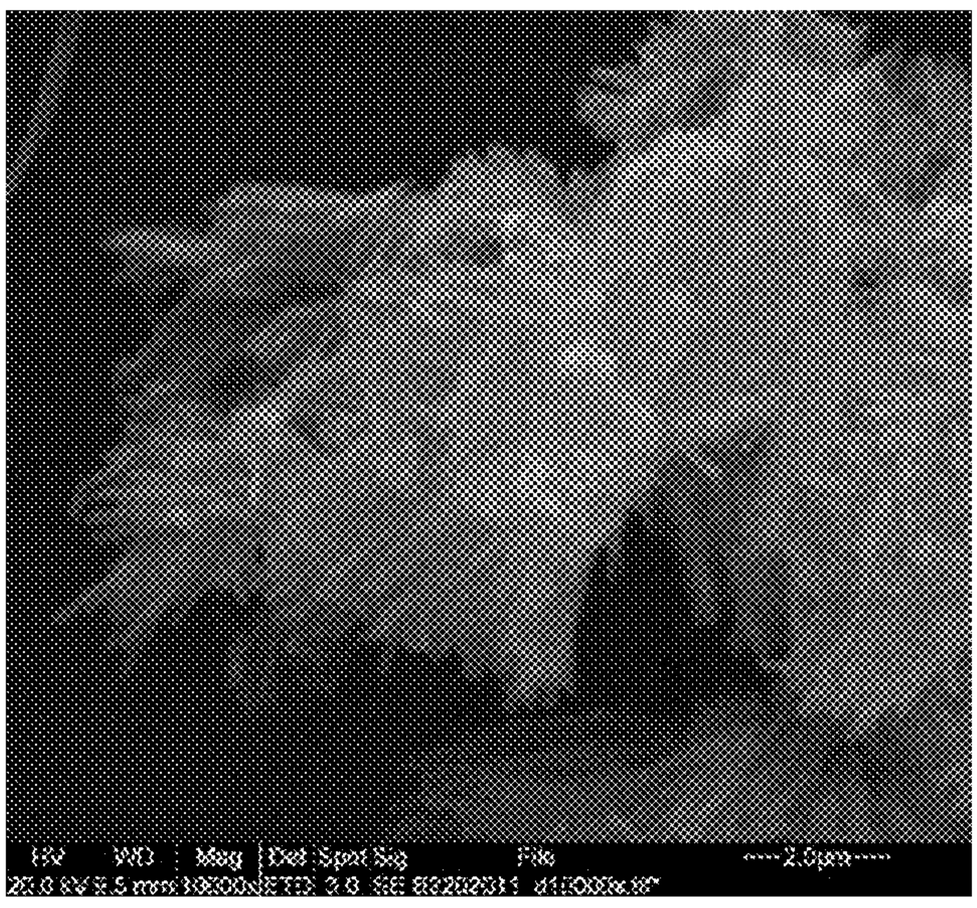
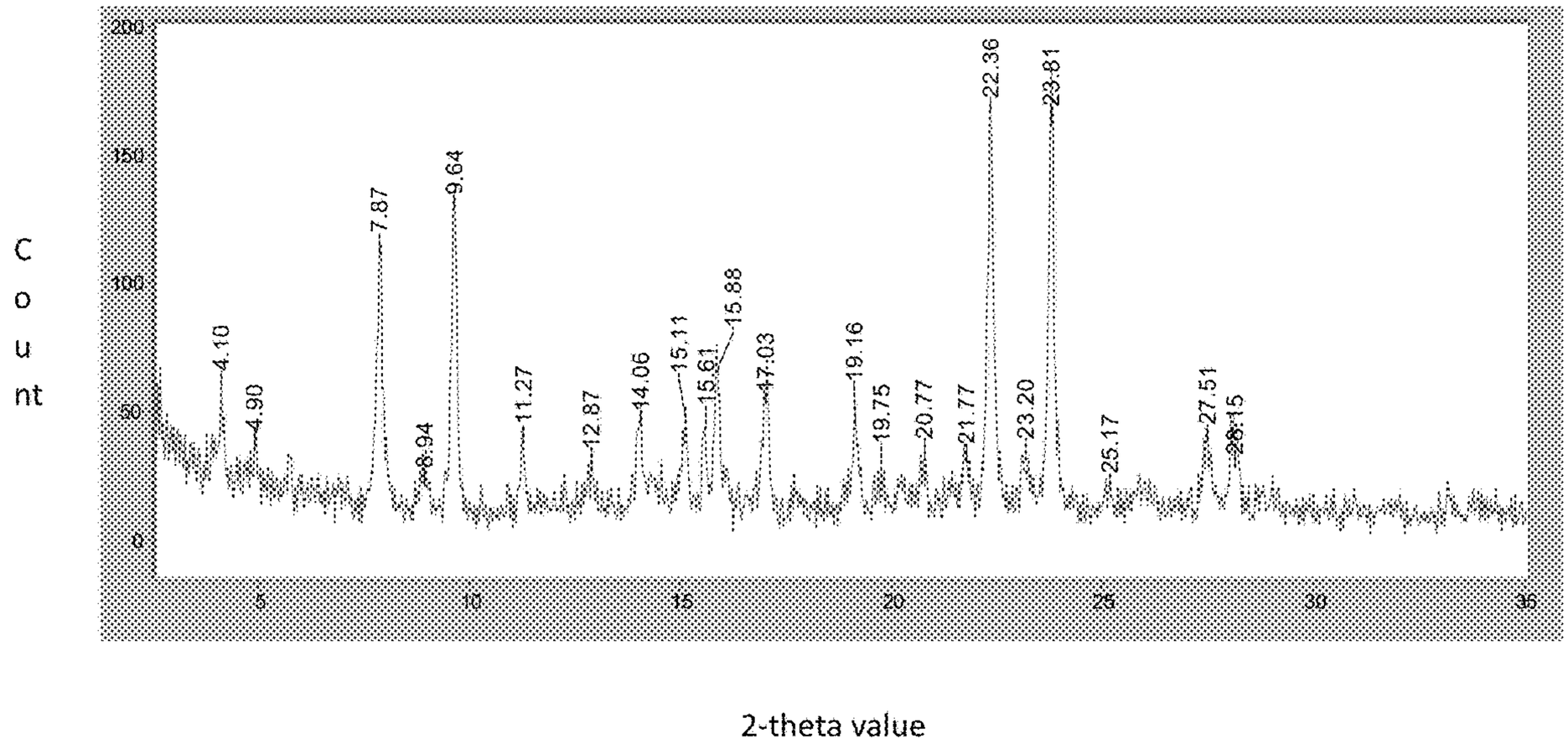

HV WD Mag Det Spot Sig File
2.0µm

FIG. 16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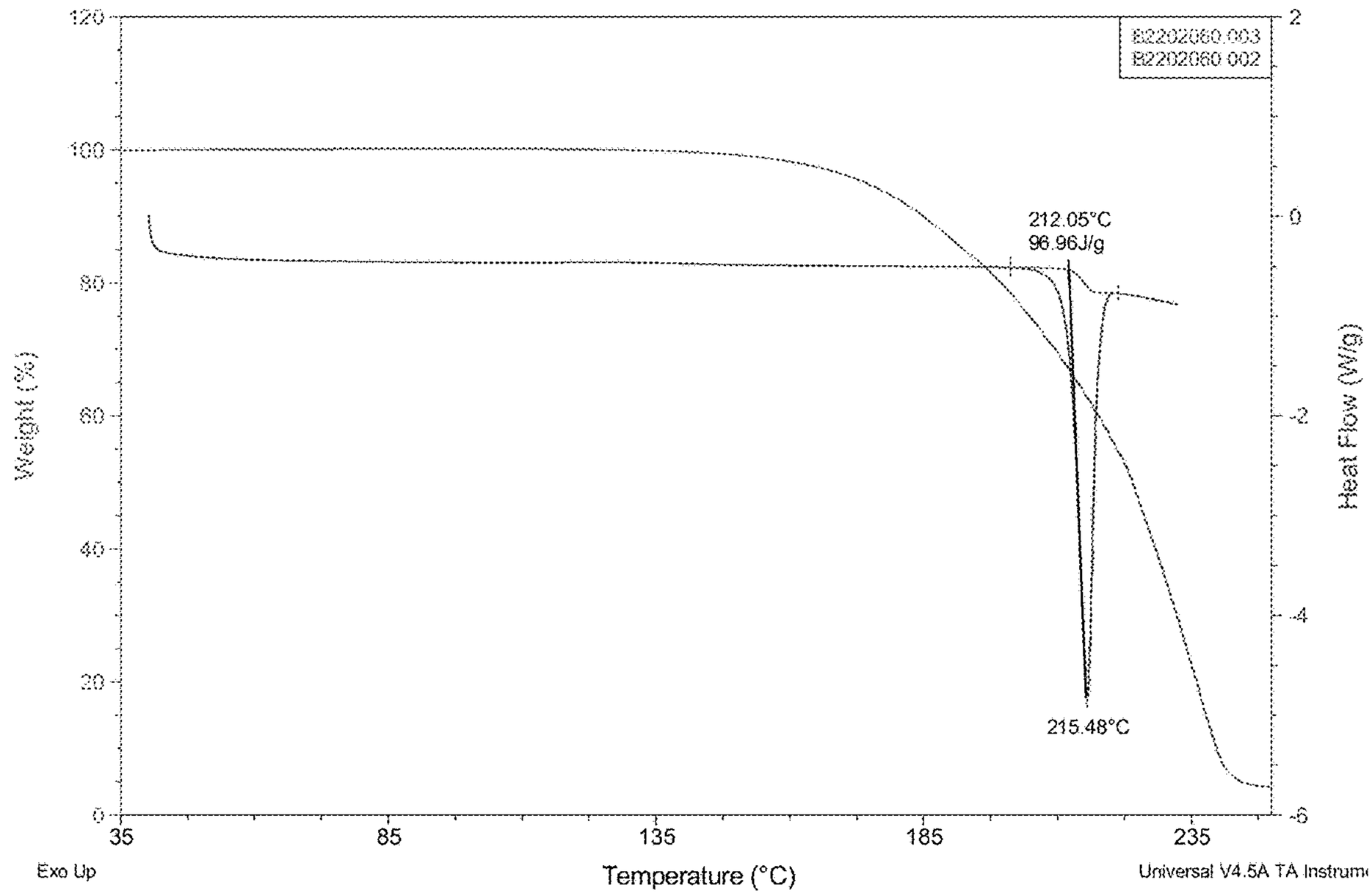
28.15

FIG. 17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40
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Weight (%)
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-2
-4
-6
Heat Flow (W/g)
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B2202080.002
212.05°C
96.96J/g
215.48°C
35
85
135
185
235
Exo Up
Temperature (°C)
Universal V4.5A TA Instrume

FIG. 18

CRYSTAL FORMS OF TETRAHYDRO-N, N-DIMETHYL-2, 2-DIPHENYL-3-FURANMETHANAMINE, PROCESSES OF MAKING SUCH FORMS, AND THEIR PHARMACEUTICAL COMPOSITIONS

CROSS REFERENCED TO RELATED APPLICATIONS

[0001] This application is a divisional application of U.S. patent application Ser. No. 17/222,611 filed Apr. 5, 2021; which is a continuation of U.S. patent application Ser. No. 16/525,319 filed Jul. 29, 2019; which is a divisional of U.S. patent application Ser. No. 15/579,705 filed Dec. 5, 2017, which is the 35 U.S.C. 371 National Stage of International Application Number PCT/IB2016/001181, filed Jul. 19, 2016, which claims priority from U.S. Provisional Patent Application No. 62/195,486 filed Jul. 22, 2015, the entire contents of each of which are incorporated herein by reference.

FIELD

[0002] The present disclosure is directed to crystalline forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride, as well as compositions, processes of preparation, and uses thereof.

BACKGROUND

[0003] Because improved drug formulations showing, for example, better bioavailability or better stability are consistently sought, there is an ongoing need for more fully characterized, new, polymorphic and derivative forms of drug molecules. Characterization of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride, and crystalline polymorphs and a metabolite of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride are described herein toward this end.

SUMMARY OF THE PRESENT DISCLOSURE

[0004] The present disclosure comprises crystalline forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride characterized by the PXRD pattern shown in FIG. **1**, FIG. **4**, or FIG. **8**. The crystalline forms are further characterized by the FTIR spectrum shown in FIG. **5** or FIG. **9**. The crystalline forms are further characterized by the ^{1}H-NMR spectrum shown in FIG. **6** or FIG. **10**. The crystalline forms are further characterized by the particle shapes depicted in FIG. **2**, FIG. **3**, FIG. **7** or FIG. **11**. The crystalline forms are further characterized by the particle sizes depicted in FIG. **2**, FIG. **3**, FIG. **7** or FIG. **11**. The crystalline forms can have a plate-like habit. The crystalline forms can also have a needle-like habit. The crystalline forms can have a lath-like habit. Further included, is a method of making the crystalline forms using a supercritical fluid (SCF) technique. Further included is a dosage form comprising a therapeutically neuroprotective amount of the crystalline forms. Further included is a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of the crystalline forms. Further included is a method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of the crystalline forms.

[0005] The present disclosure also comprises crystalline Form I of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride characterized by the PXRD pattern shown in FIG. **1**. The crystalline Form I according is also characterized by the particle shapes as depicted in FIG. **2**. The crystalline Form I is also characterized by the particle shapes as depicted in FIG. **3**. The crystalline Form I is also characterized by the particle sizes as depicted in FIG. **2**. The crystalline Form I is also characterized by the particle sizes as depicted in FIG. **3**. Crystalline Form I is also characterized by a plate-like habit. Further included is a method of making crystalline Form I using a supercritical fluid (SCF) technique. Further included is a dosage form comprising a therapeutically neuroprotective amount of crystalline Form I. Further included is a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of crystalline Form I. Further included is a method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of the crystalline Form I.

[0006] The present disclosure also comprises crystalline Form II of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride characterized by the PXRD pattern shown in FIG. **4**. Crystalline Form II is also characterized by the FTIR spectrum shown in FIG. **5**. Crystalline Form II is also characterized by the ^{1}H-NMR spectrum shown in FIG. **6**. Crystalline Form II is also characterized by particle shapes as depicted in FIG. **7**. Crystalline Form II is also characterized by particle sizes as depicted in FIG. **7**. Crystalline Form II can also have a plate-like habit. Further included is a method of making crystalline Form II using a supercritical fluid (SCF) technique. Further included is a dosage form comprising a therapeutically neuroprotective amount of crystalline Form II. Further included is a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of crystalline Form II. Further included is a method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of crystalline Form II.

[0007] The present disclosure also comprises crystalline Form III of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride characterized by the PXRD pattern shown in FIG. **8**. Crystalline Form III is also characterized by the FTIR spectrum shown in FIG. **9**. Crystalline Form III is also characterized by the ^{1}H-NMR spectrum shown in FIG. **10**. Crystalline Form III is also characterized by particle shapes as depicted in FIG. **11**. Crystalline Form III is also characterized by particle sizes as depicted in FIG. **11**. Crystalline Form III can also have a lath-like habit. Further included is a method of making crystalline Form III using a supercritical fluid (SCF) technique. Further included is a dosage form comprising a therapeutically neuroprotective amount of crystalline Form III. Further included is a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of crystalline Form III. Further included is a method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of crystalline Form III.

[0008] The present disclosure also comprises metabolite ANAVEX19-144 characterized by the PXRD pattern shown in FIG. **12**. Metabolite ANAVEX19-144 is also characterized by the DSC-TGA data shown in FIG. **13**. Metabolite

ANAVEX19-144 is also characterized by the FTIR spectrum shown in FIG. **14**. Metabolite ANAVEX19-144 can also be characterized by particle shapes as depicted in FIG. **15**. Metabolite ANAVEX19-144 can also be characterized by particle sizes as depicted in FIG. **15**. Metabolite ANAVEX19-144 can also have a needle-like habit. Further included is a method of making the metabolite ANAVEX19-144 using a supercritical fluid (SCF) technique. Further included is a dosage form comprising a therapeutically neuroprotective amount of the metabolite ANAVEX19-144. Further included is a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of the metabolite ANAVEX19-144. Further included is a method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of the metabolite ANAVEX19-144.

[0009] The present disclosure also comprises metabolite ANAVEX19-144 characterized by the PXRD pattern shown in FIG. **17**. Metabolite ANAVEX19-144 is also characterized by the DSC-TGA data shown in FIG. **18**. Metabolite ANAVEX19-144 can also be characterized by particle shapes as depicted in FIG. **16**. Metabolite ANAVEX19-144 can also be characterized by particle sizes as depicted in FIG. **16**. Further included is a method of making the metabolite ANAVEX19-144 using a supercritical fluid (SCF) technique. Further included is a dosage form comprising a therapeutically neuroprotective amount of metabolite ANAVEX19-144. Further included is a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of metabolite ANAVEX19-144. Further included is a method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of metabolite ANAVEX19-144.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] In order to describe the manner in which the advantages and features of the disclosure can be obtained, reference is made to embodiments thereof which are illustrated in the appended drawings. Understanding that these drawings depict only exemplary embodiments of the disclosure and are not therefore to be considered to be limiting of its scope, the principles herein are described and explained with additional specificity and detail through the use of the accompanying drawings in which:

[0011] FIG. **1** depicts a powder X-ray diffraction (PXRD) pattern characteristic of polymorph Form I of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0012] FIG. **2** depicts scanning electron microscope (SEM) micrographs demonstrating the size and morphology of particles of polymorph Form 1 of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) produced using acetonitrile as the solvent in the supercritical fluid process;

[0013] FIG. **3** depicts SEM micrographs demonstrating the size and morphology of particles of polymorph Form 1 of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) produced using ethanol as the solvent in the supercritical fluid process;

[0014] FIG. **4** depicts a PXRD pattern characteristic of polymorph Form II of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0015] FIG. **5** depicts a fourier transform infrared (FTIR) spectrum characteristic of polymorph Form II of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0016] FIG. **6** depicts a proton nuclear magnetic resonance (^{1}H-NMR) spectrum characteristic of polymorph Form II of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0017] FIG. **7** depicts SEM micrographs demonstrating the size and morphology of particles of polymorph Form II of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0018] FIG. **8** depicts a PXRD pattern characteristic of polymorph Form III of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0019] FIG. **9** depicts an FTIR spectrum characteristic of polymorph Form III of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0020] FIG. **10** depicts a ^{1}H-NMR spectrum characteristic of polymorph Form III of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0021] FIG. **11** depicts SEM micrographs demonstrating the size and morphology of particles of polymorph Form III of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73);

[0022] FIG. **12** depicts a PXRD pattern characteristic of metabolite ANAVEX19-144 produced using ethanol as the solvent in the supercritical fluid process;

[0023] FIG. **13** depicts DSC-TGA data characteristic of metabolite ANAVEX19-144 produced using ethanol as the solvent in the supercritical fluid process;

[0024] FIG. **14** depicts a FTIR spectrum characteristic of metabolite ANAVEX19-144 produced using ethanol as the solvent in the supercritical fluid process;

[0025] FIG. **15** depicts SEM micrographs demonstrating the size and morphology of particles of metabolite ANAVEX19-144 produced using ethanol as the solvent in the supercritical fluid process;

[0026] FIG. **16** depicts SEM micrographs demonstrating the size and morphology of particles of metabolite ANAVEX19-144 produced using dichloromethane as the solvent in the supercritical fluid process;

[0027] FIG. **17** depicts a PXRD pattern characteristic of metabolite ANAVEX19-144 produced using dichloromethane as the solvent in the supercritical fluid process; and

[0028] FIG. **18** depicts DSC-TGA data characteristic of metabolite ANAVEX19-144 produced using dichloromethane as the solvent in the supercritical fluid process.

DETAILED DESCRIPTION

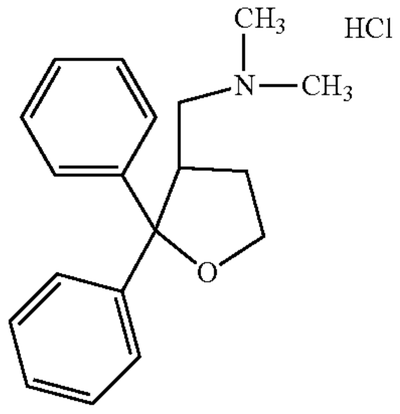
[0029] Various embodiments of the disclosure are discussed in detail below. While specific implementations are discussed, it should be understood that this is done for illustration purposes only. A person skilled in the relevant art will recognize that other components and configurations may be used without parting from the spirit and scope of the disclosure.

[0030] It should be understood at the outset that although illustrative implementations of one or more embodiments are illustrated below, the disclosed method may be implemented using any number of techniques. The disclosure should in no way be limited to the illustrative implementations, drawings, and techniques illustrated herein, but may

be modified within the scope of the appended claims along with their full scope of equivalents.

[0031] In the following discussion and in the claims, the terms "including" and "comprising" are used in an open-ended fashion, and thus should be interpreted to mean "including, but not limited to . . . ". The various characteristics described in more detail below, will be readily apparent to those skilled in the art with the aid of this disclosure upon reading the following detailed description, and by referring to the accompanying drawings.

[0032] The present disclosure relates to tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride, also referred to as ANAVEX2-73:



[0033] It has been reported that ANAVEX2-73 shows neuroprotective potential against amyloid toxicity in mice. In particular, ANAVEX2-73 has been reported as attenuating oxidative stress, caspases induction, cellular loss and learning and memory deficits observed in mice one week after the i.c.v. injection of an oligomeric preparation of amyloid β_{25-35} peptide ($A\beta_{25-35}$). See J. Psychopharmacol. 25(8), 1101-1117 (2011). More recently, it has been reported that ANAVEX2-73 blocked the $A\beta_{25-35}$-induced P-Akt decrease and P-GSK-3β increase, indicating activation at the PI3K neuroprotective pathway. See Neuropsychopharmacology 38, 1706-1723

[0034] In the dose-range tested, ANAVEX2-73 attenuated the hyperphosphorylation of Tau on physiological epitopes (AT-8 antibody clone) and on pathological epitopes (AT-100 clone). ANAVEX2-73 also has been reported to decrease the $A\beta_{25-35}$-induced endogenous $A\beta_{1-42}$ seeding.

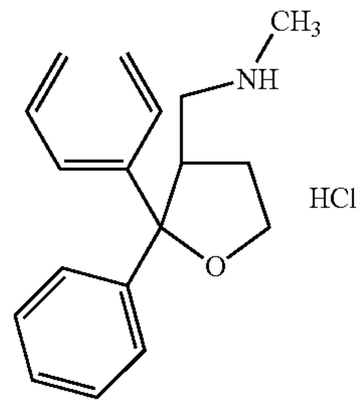
[0035] Reference is made to U.S. Patent Publication No. 2014/0296211 entitled "ANAVEX2-73 AND CERTAIN ANTICHOLINESTERASE INHIBITORS COMPOSITION AND METHOD FOR NEUROPROTECTION," to Vamvakides et al., filed Jul. 12, 2013; U.S. Ser. No. 62/065,833 entitled "A19-144, A2-73 AND CERTAIN ANTICHOLINESTERASE INHIBITOR COMPOSITIONS AND METHOD FOR ANTI-SEIZURE THERAPY," filed Oct. 20, 2014; U.S. Patent application entitled "ANAVEX2-73 FOR THE TREATMENT OF ALZHEIMER'S DISEASE" and filed on date even herewith; U.S. Patent application entitled "ENANTIOMERS OF A2-73, ANALOGUES, AND SIGMA AGONIST ACTIVITY" and filed on date even herewith. The teaching of these applications and publications and all references cited herein are incorporated by reference in their entirety.

[0036] The present disclosure, provides a crystalline polymorph (Form I) of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride, characterized by PXRD and other data provided herein.

[0037] The present disclosure provides another crystalline polymorph (Form II) of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride characterized by the PXRD and other data provided herein.

[0038] The present disclosure further provides another crystalline polymorph (Form III) of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride characterized by the PXRD and other data provided herein.

[0039] The present disclosure also provides a metabolite of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride, referred to as ANAVEX19-144, characterized by the PXRD and other data provided herein and having the structure:



[0040] The present disclosure further provides use of the polymorphs and metabolite material in the treatment of Alzheimer's disease.

[0041] Tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) was characterized by powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), fourier transform infrared (FTIR) spectroscopy, proton nuclear magnetic resonance (^{1}H-NMR) and scanning electron microscopy (SEM), as detailed in FIGS. **1-15**.

[0042] The present disclosure further provides processes of preparing the polymorphic forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73). In one embodiment, the polymorphic forms, disclosed herein, can be prepared by a supercritical fluid (SCF) anti-solvent process. In an embodiment, the anti-solvent is a supercritical fluid, although in some embodiments near-critical fluids may also be suitable. A "supercritical fluid" is a fluid at or above its critical pressure (Pc) and critical temperature (Tc) simultaneously. In practice, the pressure of the fluid is likely to be in the range between 1.01 and 7.0 of its critical pressure, and its temperature in the range between 1.01 and 4.0 of its critical temperature (in Kelvin). However, some fluids (e.g., helium and neon) have particularly low critical pressures and temperatures, 10 and may need to be used under operating conditions well in excess of those critical values, such as up to 200 times the relevant critical value. The term "near-critical fluid" encompasses both high pressure liquids, which are fluids at or above their critical pressure but below (although preferably close to) their critical temperature, and dense vapors, which are fluids at or above their critical 15 temperature but below (although preferably close to) their critical pressure. By way of example, a high pressure liquid might have a pressure between about 1.01 and 7 times its Pc, and a temperature between about 0.5 and 0.99 times its Tc. A dense vapor might, correspondingly, have a pressure

between about 0.5 and 0.99 times its Pc, and a temperature between about 1.01 and 4 times its Tc.

[0043] Suitably, the anti-solvent and solution may be introduced into a precipitation chamber via respective passages with respective outlets, the outlets being arranged relative to one another such that anti-solvent introduced through a first passage and solution introduced through a second passage both enter the precipitation chamber at substantially the same point, which is substantially the point at which the anti-solvent and solution meet. To provide for good levels of mixing and dispersion, the anti-solvent and the solution may, for example, be co-fed into a precipitation chamber via a nozzle having co-axial passages which terminate adjacent to one another. Alternatively, one or more streams of the antisolvent may be arranged to impinge on a stream of the solution to provide good levels of mixing and dispersion. However, other mixing architectures are also possible. Examples of suitable apparatus are known, inter alia, from WO-30 95/01221, WO-96/00610, WO-98/36825, WO-99/44733, WO-99/59710, WO-01/03821, and WO-03/008082, which are incorporated herein by reference.

[0044] According to the present disclosure, new crystalline forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) were prepared by a supercritical fluid (SCF) process. The basic process involved preparing a solution of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) in a suitable solvent, such as acetonitrile or ethanol, and introducing the solution to an SCF environment, typically supercritical CO_2, in a pressure vessel. The supercritical CO_2 acted as a powerful antisolvent allowing particles to be rapidly precipitated. Different polymorphic forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) were produced by manipulating SCF process parameters, including the solvent used, flow rate, pressure, and temperature. Additionally, manipulation of SCF process parameters determined the size, morphology, and habit of crystalline particles produced by the SCF process.

[0045] The SCF process parameters used to produce the three polymorphic forms of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73), Forms I-III, are provided in Tables 1-3. As shown in Table 1, crystalline Form I was produced by placing the ANAVEX2-73 starting material in a solvent of acetonitrile or ethanol and processed by the supercritical fluid technique. The resulting particle shape differed depending upon the solvent. The particle shape for the crystalline Form I produced using acetonitrile solvent was plate-like. As used herein, the term "plate-like" refers to a flat particle of similar length and width. The particle shape for the crystalline Form I produced using ethanol solvent was a conglomerate. As used herein, the term "conglomerate" refers to a mixture of two or more types of particle shapes. The resulting material was characterized by PXRD and SEM. The PXRD for crystalline Form I of ANAVEX2-73 is shown in FIG. **1**. SEM micrographs showing the particle size and morphology of crystalline Form I are shown in FIGS. **2-3**. FIG. **2** shows the particle size and morphology of crystalline Form I produced using acetonitrile solvent (plate-like morphology). FIG. **3** shows the particle size and morphology of crystalline Form I produced using ethanol as the solvent (conglomerate morphology).

[0046] As shown in Table 2, crystalline Form II was produced by placing the ANAVEX2-73 starting material in a solvent of acetonitrile, 1:9 v/v trifluoroethanol+ethanol, 1:1 v/v acetone+ethanol, or 3-methyl-1-butanol, and processed by the supercritical fluid technique. In all cases, crystalline Form II was characterized by a plate-like habit. The resulting material was characterized by PXRD and SEM. The PXRD for crystalline Form II of ANAVEX2-73 is shown in FIG. **4**. Crystalline Form II is further characterized by the FTIR spectrum shown in FIG. **5** and the ^{1}H-NMR shown in FIG. **6**. SEM micrographs showing the particle size and morphology of crystalline Form II are shown in FIG. **7**.

[0047] As shown in Table 3, crystalline Form III was produced by placing the ANAVEX2-73 starting material in a solvent of ethanol or 1:9 v/v trifluoroethanol+ethanol and processed by the supercritical fluid technique. In all cases, crystalline Form III was characterized by a lath-like habit. As used herein, "lath-like" refers to a long, thin blade-like particle. The resulting material was characterized by PXRD and SEM. The PXRD for crystalline Form III of ANAVEX2-73 is shown in FIG. **8**. Crystalline Form III is further characterized by the FTIR spectrum shown in FIG. **9** and the ^{1}H-NMR shown in FIG. **10**. SEM micrographs showing the particle size and morphology of crystalline Form III are shown in FIG. **11**.

TABLE 2

Crystalline Form II Samples

SCF sample No	Solvent	Solution Conc (mg/ml)	P (bar)	T ° C.	density (g/cm^3)	TS flow (g/min)	CO^2 flow (g/min)	mole fraction CO_2	mole fraction sol	Mass Ratio Flows	Particle shape	Surface characteristics
B2201017	acetonitrile	27.3	85	40	0.354	0.9432	20	0.955	0.045	21.20	plate	smooth
B2201018	acetonitrile	27.3	200	40	0.84	0.9432	20	0.955	0.045	21.20	plate	smooth
B2201020	acetonitrile	27.3	200	80	0.594	0.9432	20	0.955	0.045	21.20	plate	smooth
B2201028	acetonitrile	27.3	85	40	0.354	1.5720	20	0.927	0.073	12.72	plate	smooth
B2201039	acetonitrile	13	105	60	0.322	1.5720	20	0.927	0.073	12.72	plate	smooth
B2201052	1:9 v/v trifluoroethanol + ethanol	50	85	40	0.354	1.0120	20	0.952	0.048	19.76	plate	smooth
B2201053	1:9 v/v trifluoroethanol + ethanol	50	85	40	0.354	1.0120	20	0.952	0.048	19.76	plate	smooth
B2201055	1:9 v/v trifluoroethanol + ethanol	50	200	40	0.84	0.1687	20	0.992	0.008	118.57	plate	smooth

TABLE 2-continued

Crystalline Form II Samples

SCF sample No	Solvent	Solution Conc (mg/ml)	P (bar)	T ° C.	density (g/cm^3)	TS flow (g/min)	CO^2 flow (g/min)	mole fraction CO_2	mole fraction sol	Mass Ratio Flows	Particle shape	Surface characteristics
B2201057	1:9 v/v trifluoroethanol + ethanol	20	200	40	0.84	1.6867	20	0.922	0.078	11.86	plate	smooth
B2201067	1:1 v/v acetone + ethanol	50	85	40	0.354	1.5800	20	0.927	0.073	12.66	plate	smooth
B2201072	1:1 v/v acetone + ethanol	50	200	40	0.84	1.5800	20	0.927	0.073	12.66	plate	smooth
B2201076	3-methyl-1-butanol	10	85	40	0.354	0.9725	20	0.954	0.046	20.57	plate	smooth
B2201077	3-methyl-1-butanol	10	85	40	0.354	1.6208	20	0.925	0.075	12.34	plate	smooth

TABLE 1

Crystalline Form I Samples

SCF sample No	Solvent	Solution Conc (mg/ml)	P (bar)	T ° C.	density (g/cm^3)	TS flow (g/min)	CO_2 flow (g/min)	mole fraction CO_2	mole fraction sol	Mass Ratio Flows	Particle shape	Surface characteristics
B2202022	acetonitrile	27.3	105	60	0.322	0.4716	20	0.977	0.023	42.41	plate	smooth
B2202038	ethanol	40	125	80	0.318	0.0789	20	0.996	0.004	253.49	conglomerate	N/A

TABLE 3

Crystalline Form III Samples

SCF sample No	Solvent	Solution Conc (mg/ml)	P (bar)	T ° C.	density (g/cm^3)	TS flow (g/min)	CO_2 flow (g/min)	mole fraction CO_2	mole fraction sol	Mass Ratio Flows	Particle shape	Surface characteristics
B2201011	ethanol	40	85	40	0.354	0.4734	20	0.977	0.023	42.25	lath	smooth
B2201036	ethanol	40	200	40	0.84	1.5780	20	0.927	0.073	12.67	lath	smooth
B2201054	1:9 v/v trifluoroethanol + ethanol	50	85	40	0.354	0.1687	20	0.992	0.008	118.57	lath	cracked

[0048] The present disclosure also provides a metabolite of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride, ANAVEX19-144. ANAVEX19-144 has documented anti-amnesic and neuroprotective potentials similar to ANAVEX2-73. See for example J. of Psychopharmacol. 25(8), 1101-1117 (2011). Crystalline forms of ANAVEX19-144 were produced by placing the ANAVEX19-144 starting material in a solvent of ethanol or dichloromethane and processed by the supercritical fluid technique. The crystalline form of ANAVEX19-144 produced by the supercritical fluid technique under process parameters of 40 mg/mL ethanol solution, 200 bars of pressure, temperature of 80° C., supercritical CO_2 solution with a flow rate of 20 g/min and a TS flow of 0.4 mL/min, was characterized by PXRD, FTIR, DSC, and SEM, as shown in FIGS. **12-15**. As shown in FIG. **15**, the crystalline form of ANAVEX19-144 was characterized by needle-like crystals. In contrast, the crystalline form of ANAVEX19-144 produced by similar process parameters using the solvent dichloromethane exhibited a mixed habit of needle-like and lath-type particles, as shown in FIG. **16**. The crystalline form of ANAVEX19-144 produced using the dichloromethane supercritical fluid technique produced a powder with better flow characteristics and improved flow properties for downstream processing. The crystalline form of ANAVEX19-144 was further characterized by PXRD and DSC, as shown in FIGS. **17-18**. The two crystalline forms of ANAVEX19-144, produced according to the supercritical fluid technique in ethanol or dichloromethane were stored at 40° C. at 75% relative humidity in uncapped vessels for 1 week and then characterized by PXRD to determine stability of the two forms. After one week, the PXRDs for the two forms did not show any differences and therefore indicated that the two forms were stable under the conditions tested.

What is claimed is:

1. A crystal form of tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) made by crystallizing ANAVEX2-73 in a supercritical fluid (SCF) environment,

wherein the supercritical fluid comprises supercritical carbon dioxide; and

wherein the crystal form is substantially characterized by an X-ray diffraction pattern of FIG. **1**, FIG. **4**, or FIG. **8**.

2. The crystal form of claim **1**, wherein the crystallizing comprises:

a. making a solution of ANAVEX2-73 in a solvent;

b. introducing the solution to the SCF;

c. allowing crystallization of ANAVEX2-73 in the SCF environment to form crystals; and

d. isolating the crystals, thus obtaining the crystal form.

3. The crystal form of claim **2**, wherein the solvent comprises ethanol, acetonitrile, isopropyl alcohol, trifluoroethanol, acetone, 2-ethoxyethanol, 1-propanol, dichloromethane, dimethyl sulfoxide, N,N'-dimethylacetamide, dimethylformamide, trifluoroethanol, 1:9 v/v trifluoroethanol+ethanol, 1:1 v/v acetone+ethanol, 3-methyl-1-butanol, N-methyl-2-pyrrolidone, tert-butanol, or a combination thereof.

4. The crystal form of claim **2**, wherein the SCF environment comprises pressure from about 85 bar to about 200 bar, and temperature ranging from about 40° C. to about 80° C.

5. The crystal form of claim **1**, further characterized by the FTIR spectrum of FIG. **5** or FIG. **9**.

6. The crystal form of claim **1**, further characterized by the particle shapes of FIG. **2**, FIG. **3**, FIG. **7** or FIG. **11**.

7. The crystal form of claim **1**, further characterized by a plate-like, conglomerate-like, or lath-like habit.

8. The crystal form of claim **1**, wherein the crystal form comprises

i. Crystal Form I, which is substantially characterized by the X-ray diffraction pattern of FIG. **1**, and particle size and morphology as shown in FIG. **2** or FIG. **3**.

ii. Crystal Form II; which is substantially characterized by the X-ray diffraction pattern of FIG. **4**, and the FTIR spectrum of FIG. **5**; or

iii. Crystal Form III, which is substantially characterized by the X-ray diffraction pattern of FIG. **8**, and the FTIR spectrum of FIG. **9**.

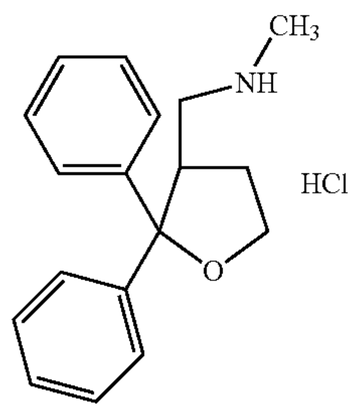
9. The crystal form of claim **8**, wherein

i. The Crystal Form II is further characterized by the particle size and morphology as shown in FIG. **7**; or

ii. The Crystal Form III is further characterized by the particle size and morphology as shown in FIG. **11**.

10. A method of making a crystal form of ANAVEX19-144 represented by Formula I, comprising crystallizing the ANAVEX19-144 in a supercritical fluid (SCF) environment.

Formula I



11. The method of claim **10**, wherein the SCF comprises supercritical carbon dioxide.

12. The method of claim **10**, wherein the crystallizing comprises:

a. making a solution of ANAVEX19-144 in a solvent;

b. introducing the solution to the SCF;

c. allowing crystallization of ANAVEX19-144 in the SCF environment to form crystals;

d. isolating the crystals, thus obtaining the crystal form of ANAVEX19-144.

13. The method of claim **12**, wherein the solvent comprises ethanol, 2-ethoxyethanol, 1-propanol, acetone, acetonitrile, isopropyl alcohol, dichloromethane, dimethyl sulfoxide, trifluoroethanol, N,N'-dimethylacetamide, dimethylformamide, 1:9 v/v trifluoroethanol+ethanol, 1:1 v/v acetone+ethanol, 3-methyl-1-butanol, N-methyl-2-pyrrolidone, tert-butanol, or any combination thereof.

14. The method of claim **12**, wherein the SCF environment comprises pressure at 200 bars, temperature at about 80° C., and supercritical CO_2 solution with a flow rate of about 20 g/min.

15. A crystal form produced according to the method of claim **10**, substantially characterized by an X-ray diffraction pattern of FIG. **12** or FIG. **17**.

16. The crystal form of claim **15**, further characterized by DSC-TGA of FIG. **13** or FIG. **18**.

17. The crystal form of claim **15**, further characterized by particle shapes of FIG. **15** or FIG. **16**.

18. The crystal form of claim **15**, further characterized by a needle-like habit, a lath-like habit, or a combination thereof.

19. Use of the crystal form of claim **1** in the preparation of a medicament for the treatment of Alzheimer disease.

20. Use of the crystal form of claim **10** in the preparation of a medicament for the treatment of Alzheimer disease.

* * * * *